

Bon Secours Richmond  
Pharmacy & Therapeutics Committee  
Direct Thrombin Inhibitors  
2/2003

Recommendations: MEC approved

- Bivalirudin (Angiomax) is recommended for formulary inclusion for use in the cardiac cath lab during PCIs.
- Lepirudin (Refludan) is recommended for removal from the formulary due to:
  - Complexity of dosing and administration
  - Antigenic potential. Shock and death have been reported in post marketing surveillance due to anaphylaxis with initial administration or upon second or subsequent re-exposures.
  - Lepirudin is an irreversible thrombin inhibitor; a reversing agent is not available. Half-life is dependent on renal function and the half-life is approximately 2 days in renal insufficiency.
  - Lepirudin is not recommended for use in patients with a creatinine clearance < 30 ml/min.
  - If ordered, pharmacy will confirm that the patient's creatinine clearance is greater than 30 ml/min before dispensing lepirudin and will monitor the patient's renal function during therapy.
- Argatroban is recommended for formulary inclusion and is recommended to be used in place of lepirudin. Both are FDA approved for prophylaxis and treatment of thrombosis in patients with HIT. Argatroban is hepatically cleared with a half-life of 1-3 hours.

**Bivalirudin (Angiomax)**

REPLACE-2 Study

A double blind multicenter placebo control trial of 6002 patients undergoing PCI

	Bivalirudin	Heparin plus 2b3a Inhibitors
Number of patients	3008	2994
Heparin	None	65 units/kg, additional 20 units/kg if ACT < 225 at 5 minutes (required in 12%)
Bolus	0.75 mg/kg, additional 0.3 mg/kg if ACT < 225 at 5 minutes (required in 2.9%)	Eptifibatide 180 mcg/kg double bolus, Abciximab: 0.25 mg/kg bolus
Continuous Infusion	1.75 mg/kg/hr during PIC or up to 4 hours at discretion of investigator	Eptifibatide 2 mcg/kg/min 18-24 hours or Abciximab 0.125 mcg/kg/min for 12 hours
Duration		12-18 hours
Provisional 2b3a inhibitor add on	7.2%	5.2%
<b>Outcome Data</b>		
Quadruple Endpoint (Death, MI, Revascularization, Major Bleed) at 30 days	9.2%	10% NS p=0.32
Triple (Death, MI, Revascularization) at 30 days	7.6%	7.1% NS p=0.4
Death	0.2%	0.4% NS p=0.255
MI	7%	6.2% NS p=0.243
Urgent Revascularization	1.2%	1.4% NS p=0.435
Major Bleed (Intracranial, retroperitoneal, or overt bleeding with a drop of Hgb drop $\geq$ 3 g/dl or leading to transfusion of $\geq$ 2 units RBCs, or a drop in Hgb $\geq$ 4 g/dl with no observed bleeding.	2.4%	4.1% P<0.001
Minor Bleed	13.4%	25.7% P<0.001
Sheath Bleed	0.8%	2.5% P<0.001
Retroperitoneal	0.2%	0.6% NS
Thrombocytopenia (<100 K)	0.7%	1.7% P < 0.001
Transfusion	1.7%	2.5% P=0.021
<b>Economic Analysis</b>		
Patient Cost	82% 1 vial, 18% 2 vials \$325-\$650 per patient	\$540-\$710 for Integrelin

**Findings:**

- FDA approved in 12/2000 for PTCA in USA along with aspirin 325 mg/day.
- Bivalirudin initially acts as a noncompetitive antagonist to thrombin, binding to the catalytic site on thrombin. It also binds competitively to the fibrinogen-binding site. Thrombin recognized bivalirudin as a substrate and cleaves it from catalytic site leaving bivalirudin bound to the fibrinogen-binding site, which acts as a competitive inhibitor to thrombin.
- ACT values correlate well with dose, but ACT values are not predictive of ischemic or hemorrhagic complications. These same studies showed no correlation of heparin ACT and major hemorrhage.
- Incompatible at y-site with alteplase, amiodarone, amphotericin B, chlorpromazine, diazepam, prochlorperazine, reteplase, streptokinase, and vancomycin.
- Bleeding increases with decreasing renal function but is less than heparin.
- ACT should be monitored in patients with renal impairment (creatinine clearance < 60 ml/min).
- Two studies have used Angiomax along with a 2b3a inhibitor. Data from the larger study is included below.

**Bivalirudin COMPARATIVE EFFICACY:**

**Package Insert Data for Bivalirudin (Angiomax) Use During PTCA**

<b>Incidences of In-hospital Clinical Endpoints in Randomized Clinical Trials Occurring within 7 days</b>		
<b>Efficacy Endpoints for All Patients</b>	<b>Bivalirudin N=2161</b>	<b>Heparin N 2151</b>
Dosage	<i>1 mg/kg load, 2.5 mg/kg/hr x 4 hours, then 0.2 mg/kg/hr for up to 20 hours (average duration 14 hours)</i>	175 U/kg loading then 15 u/kg/hr for up to 24 hours, additional bolus of 60 u/kg if ACT < 350 seconds
Composite endpoint of death or MI or clinical deterioration of cardiac organ requiring revascularization or IABP or abrupt vessel closure	7.9%	9.3%
Death, MI, Revascularization	6.2%	7.9% p=0.039
Death	0.2%	0.2%
MI	3.3%	4.2%
Revascularization: any revascularization procedure, including angioplasty, CABG, stenting, or IABP)	4.2%	5.6% p=0.03
Major Hemorrhage	3.5%	9.3% p < 0.001
With >= 3 gm/dl fall in Hgb	1.9%	5.8% p < 0.001
With >= 5 gm/dl fall in Hgb	<1%	2.2% p < 0.001
ICB	<1%	<1% NS
Required Transfusion	2%	5.7% p < 0.001
Median LOS (days)	4	4
Initial ACT	345	382

Bleeding rates in the heparin group may have been increased as no ACT values were monitored once ACT target was achieved.

*Exclusion criteria included: serum creatinine > 3 mg/dl, thrombolytic therapy within the previous 24 hours, scheduled to undergo coronary atherectomy, stenting, or laser angioplasty or staged angioplasty and pregnancy.*

*Femoral sheaths were removed 2 hours after the infusion of study drug was discontinued.*

Cost of bivalirudin therapy \$1001 for first 4 hours, \$1300 to complete therapy for a 70 kg patient.

**Angioplasty**

**Hirulog Angioplasty Study**

Bivalirudin and heparin were compared in a double-blind trial enrolling 4,098 patients undergoing angioplasty for unstable or postinfarction angina (the Hirulog Angioplasty Study 1993). Bivalirudin or heparin was administered immediately before angioplasty. *Bivalirudin was dosed as a 1 mg/kg bolus followed by a 4-hour infusion of 2.5 mg/kg/h and a 14- to 20-hour infusion at a rate of 0.2 mg/kg/h. (This is not the dose currently recommended by the company). Concurrent 2b3a inhibitors (tirofiban, eptifibatide, and abciximab) were not used. Heparin was dosed as a bolus dose of 175 units/kg followed by an 18- to 24-hour infusion at a rate of 15 units/kg/h. The heparin dose was adjusted based on the ACT drawn at 5 minutes and 45 minutes. If the ACT was less than 350 seconds, the bivalirudin group was given a bolus of saline and the heparin group was given a bolus of 60 units/kg of heparin. Aspirin (300 to 325 mg) was given to all patients. The primary study end point was death, myocardial infarction (MI), abrupt vessel closure, or rapid clinical deterioration of cardiac origin during hospitalization requiring CABG, IAB. Exclusion criteria included: serum creatinine > 3 mg/dl, thrombolytic therapy within the previous 24 hours, scheduled to undergo coronary atherectomy, stenting, or laser angioplasty or staged angioplasty and pregnancy.* The incidence of the primary end point in the intend-to-treat cohort did not differ between the treatment groups (11.8% with bivalirudin vs 12.9% with heparin; p=0.26). Bivalirudin therapy had a lower incidence of bleeding compared to heparin. Bivalirudin was associated with a lower incidence of retroperitoneal hemorrhage (0.2% vs 0.7%, p=0.02), need for transfusion (3.7% vs 8.6%, p<0.001), and major hemorrhage (3.8% vs 9.8%, p<0.001). The cumulative rate of death, MI, and repeated revascularization in the 6 months after angioplasty did not differ; 25.7% with bivalirudin and 26.6% with

heparin in the intend-to-treat cohort (p=0.54), and 20.5% with bivalirudin and 25.1% with heparin in the patients with postinfarction angina (p=0.17). In the subgroup of 704 patients with postinfarction angina, bivalirudin therapy was associated with a lower incidence of the primary end point (9.1% vs 14.2%, p=0.04) and a lower incidence of major bleeding (3% vs 11.1%, p<0.001) and minor bleeding (52.3% vs 68%, p<0.001). As in the larger study population, rates of death, MI, and repeated revascularization in the 6 months following study drug administration did not differ. In another subgroup of 567 patients with thrombus-containing lesions, the incidence of the primary outcome and 6-month outcomes did not differ between treatment groups.<sup>5,6,7,8</sup> *A reanalysis of the results of this trial on an intent-to-treat basis identified 4312 patients, 2161 of whom were treated with bivalirudin are included in the product labeling. The reanalysis used a more sensitive definition of MI than the original report.* The primary endpoint of procedural failure (death, MI, clinical deterioration of cardiac origin requiring revascularization or placement of an aortic balloon pump, or angiographic evidence of abrupt vessel closure) occurred in 7.9% of bivalirudin-treated patients compared to 9.3% of heparin-treated patients.<sup>1,9</sup>

### With 2b3a Inhibitors

Bivalirudin with planned or provisional abciximab versus low-dose heparin and abciximab during PCI: Results of the Comparison of Abciximab Complications with Hirulog for Ischemic Events Trial (CACHET)

CACHET Study Results (Open Labeled Randomized)				
	N=60	N=129	N=80	Control Arm N=94
Randomization Ratio (Control arm/study arm)	1:1	1:2	1:3	
Control arm	Low-dose weight adjusted heparin (70 u/kg) + planned abciximab			
Bivalirudin Loading mg/kg	1	0.5	0.75	
Bivalirudin infusion mg/kg/hr	2.5	1.75	1.75	
Duration of Bivalirudin (hours)	4	<i>During Procedure</i>	<i>During Procedure</i>	
Abciximab	Planned	Provisional	Provisional	Planned
Bivalirudin	N=30	N=85	N=59	N=94
ACT Mean Peak (seconds)	443	348	347	301
Death, MI, or repeat vascularization	0%(0/30)	4.7% (4/85)	0% (0/59)	6.4% (6/94)
Major Bleeding	3.3% (1/30)	2.4% (2/85)	0% (0/59)	4.3% (4/94)

Stents used in 88% of patients

### Direct Thrombin Inhibitors and HIT Findings

- HIT: heparin induced thrombocytopenia (<100,000 or > 50% fall from baseline)
- 1-2% of patients on heparin therapy for more than 4 days.
- HITTS (Heparin Induced thrombocytopenia and thrombosis syndrome): venous or arterial thrombosis along with thrombocytopenia
- Direct thrombin inhibitors inhibit both soluble and fibrin-bound thrombin.
- Bind directly to thrombin without the need for a cofactor (antithrombin III).
- Heparin can not bind to fibrin bound thrombin or platelet bound factor Xa.
- Are not inhibited by platelet factor 4 and are not associated with heparin induced thrombocytopenia (HIT).
- Do not cross react with HIT antibodies.
- *There are no antidotes for direct thrombin inhibitors.*
- Direct thrombin inhibitors and warfarin produce combined effect on INR measurements, which is dose, thrombin inhibitor and thromboplastin reagent specific. More sensitive reagents show less interference.

### Argatroban

- Studied in 568 patients with HIT/HITTS and was compared to historic controls. (see table below)
- Studied in PTCA and HIT/HITTS in 118 patients
- PTT drops to baseline 2-4 hours after infusion discontinuation.

### Lepirudin (Refludan)

- Studied in 198 patients with HIT
- *The package insert has been recently updated to include post-marketing reports of allergic and hypersensitivity reactions, including anaphylactic reactions. "Serious anaphylactic reactions that have resulted in shock or death have been reported. These reactions have been reported during initial administration or upon second or subsequent re-exposure(s)."*

Argatroban Package Insert Data						
	HIT		HITTS		HIT/ HITTS	
	Argatroban	Control	Argatroban	Control	Argatroban	Control
Composite Endpoint* Study 1	N=160 25.6%	N= 147 38.8%	N=144 43.8%	N=46 56.5%	N=304 34.2%	N=193 43%
Study 2 n=264	25.6%		41%		33.7%	
Death (Study 1)	16.9%	21.8%	18.1%	28.3%	17.4%	23.3%
Amputation (Study 1)	1.9%	2%	11.1%	8.7%	6.2%	3.6%
New Thrombosis (Study 1)	6.9%	15%	14.6%	19.6%	10.5%	16.1%

\*Composite end point: Death, amputation, new thrombosis within 37 day study period

Argatroban Major Hemorrhagic Events		
	Argatroban Study 1 & Study 2 n=568	Historic Controls n=193
Gastrointestinal	2.3%	1.6%
Genitourinary & hematuria	0.9%	0.5%
Decrease in Hgb & Hct	0.7%	0%
Multisystem hemorrhage and DIC	0.5%	1%
Limb & BKA stump	0.5%	0%
Intracranial Stump	0%	0.5%

Major Hemorrhage: Overt and associated with Hgb drop  $\geq 2$  g/dl, required  $\geq 2$  units of RBC, ICB, retroperitoneal, or into a major prosthetic joint.

Lepirudin (Refludan) Package Insert Data		
	Lepirudin (n=113)	Control (n=91)
Composite end point* at 7 days		
Study 1 n=54	3.7%	24.9%
Study 2 n=59	16.9%	
Death	4.4%	1.4%
Amputation	2.7%	2.6%
New Thrombosis	6.3%	22.2%
Composite end point* at 35 days		
Study 1	13%	47.8%
Study 2	28.9%	
Death at 35 days	8.9%	17.6%
Amputation	6.5%	10.4%
New Thrombosis	10.1%	27.2%

Composite end point: Death, amputation, new thrombosis within 7 days

Lepirudin Hemorrhagic Events		
	Lepirudin n=113	Historic Controls n=91
Hematuria	4.4%	0%
Gastrointestinal & Rectal	5.3%	6.6%
Hemothorax	0%	1.1%
Intracranial	0%	2.2%

Direct Thrombin Inhibitors

	<b>Argatroban</b>	<b>Lepirudin (Refludan)</b>	<b>Bivalirudin (Angiomax)</b>
Product	Synthetic arginine derivative	65 amino acids, Recombinant hirudin derived from yeast	20 amino acid peptide synthetic analog of hirudin
Action	Direct Thrombin Inhibitor (inhibits both free and clot- associated) univalent binding to thrombin	Direct Thrombin Inhibitor (inhibits both free and clot- associated) Bivalent binding to thrombin	Direct Thrombin Inhibitor (inhibits both free and clot-associated thrombin). Bivalent binding to thrombin.
Mechanism	Binds to thrombin active site, inhibits thrombin catalyzed or induced reactions (factors V, VIII, XIII, protein C, and platelet aggregation)	Binds to thrombin active site, inhibits thrombin catalyzed or induced reactions (factors V, VIII, XIII, protein C, and platelet aggregation)	Initially noncompetitive thrombin inhibitor and subsequently as a competitive univalent inhibitor. Does not promote platelet aggregation.
Reversible Binding To Thrombin	Yes	<b>No</b> Very slowly reversible	Yes
Antidote or Agent to Reverse Effects	No	No	No
FDA Indication(s)	Approved Anticoagulant for prophylaxis or treatment of thrombosis in patients with HIT  Patients with or at risk for heparin-induced thrombocytopenia undergoing PCI	Approved Anticoagulant for prophylaxis or treatment of thrombosis in patients with HIT	Anticoagulation in patients with USA undergoing PTCA. <i>Does not cause platelet aggregation in sera from patient with HIT/HITTS but inadequately studied in HIT/HITTS</i>
Molecular Weight (Daltons)	526	6979.5	2180
Pharmacokinetics	Linear	Linear	Linear
Time to Steady State	1-3 hours	Renal Function Dependent	
Volume of Distribution	0.174 l/kg	Extracellular fluid	0.24 l/kg
Clearance	5.1 ml/kg/min  Childs Pugh score > 6 1.9 ml/kg/min		Clcr >= 90: 3.4 ml/min/kg Clcr 60-89: 3.4 ml/min/kg Clcr 30-59: 2.7 ml/min/kg Clcr 10-29: 2.8 ml/min/kg Dialysis(off Dialysis): 1 ml/min/kg
Metabolism	<b>Liver</b>	No	Proteolytic cleavage minor amount
Route of Elimination	Biliary (14% unchanged)	<b>Kidney</b>	<b>Kidney</b>
Fraction Excreted Unchanged in Urine	16%	35%	20%
Half Life	30-51 minutes	1.3 hours (Young Health Volunteers)	25 minutes (normal renal function)
$\Delta t_{1/2}$ Renal Insufficiency Chronic renal failure	No change  Childs Pugh Score > 6 181 minutes	2 days 2- to 107 hours	Clcr > 90: 25 minutes Clcr 60-90: 22 minutes Clcr 30-59: 34 minutes Clcr 10-29: 57 minutes Clcr dialysis patients (off dialysis): 3.5 hours
Protein Binding	54%	ND	Thrombin and RBCs
Antigenic	Limited data	40% of patients develop antibodies, which prolongs the effect of the drug.	

	<b>Argatroban</b>	<b>Lepirudin (Refludan)</b>	<b>Bivalirudin (Angiomax)</b>
Monitor	APTT PCI: ACT	APTT	ACT
Effects PTT	Yes	Yes	Yes
Effects PT/INR	Yes	Yes	Yes
Effects ACT	Yes		Yes
Effects Thrombin Time	Yes	Yes	Yes
Route administration	IV	IV	IV
Dialyzable		High Flux Dialysis	25%
Loading Dose	HIT Non Cath lab No  Cath Lab HIT 350 mcg/kg over 3-5 minutes	0.4 mg/kg (for up to 110 kg) 0.2 mg/kg if clcr < 60 ml/min [0.15 mg/kg post dialysis-not FDA approved]	0.75 mg/kg bolus dose Current Recommendations from Manufacturer Not PI
Normal Infusion Dose	Non Cath Lab: 2 mcg/kg/min  Cath Lab for PCI 25 mcg/kg/min	0.15 mg/kg/hr (for up to 110 kg)	1.75 mg/kg/hr Current Recommendation from Manufacturer Not PI
Clcr 45-60 ml/min	No Change	0.075 mg/kg/hr	Clcr >= 60: 1.75 mg/kg/hr
Clcr 30-44	No Change	0.045 mg/kg/hr	Clcr 30-59: 1.4 mg/kg/hr
Clcr 15-29	No Change	0.0225 mg/kg/hr	Clcr 10-29: 0.7 mg/kg/hr
Clcr below 15	No Change	Avoid/Stop Infusion	Dialysis: 0.175 mg/kg/hr
Dose for moderate liver impairment Non Cath Lab	0.5 mcg/kg/min	None needed	None needed
PCI Patients	Not Studied		
Dosage Range	0.5-10 mcg/kg/min	0.0225-0.15 mg/kg/hr	
	Check PTT 2 hours after start of infusion or any dosage change	Check PTT 4 hours after start of infusion or any dosage change	
Therapeutic Endpoint	Non Cath Lab PTT 1.5-3 x Control (Not to exceed 100 seconds)  During PCI ACT > 300 seconds	PTT 1.5-2.5	PCI: Monitor ACT in patients with creatinine clearance < 60 ml/min. During PCI ACT > 300 seconds
How Supplied	250 mg	50 mg	250 mg
Cost per Vial	\$588	\$111.16	\$325
Usual Dilution	250 mg / 250 ml	100 mg / 250 ml	250 mg/ 50 ml
Infusion Rate for 50-120 kg	6-72 ml/hr	19-41 ml/hr	17.5-42 ml/hr
Cost per Day	\$588-4116	\$511-\$990	\$325-650 <i>per hour</i>