

BIVALIRUDIN (ANGIOMAX) VS HEPARIN FOR A PT P/W NSTEMI?

P: Admit Sr Med 9/18/08. Impression: Hypoglycemia induced syncopal episode & NSTEMI. 74 yo woman with HTN, DM2 hgb a1c 7.8, hyperlipidemia, DCM EF 25-30%, CVA with residual left sided weakness, multiple falls presents after syncopal event at home in setting of taking regular dose of insulin without eating. Impression is hypoglycemia induced syncope with this history and FS of 70 after glucose load, improved mental status. Pt also with NSTEMI in the setting of myocardial stress induced by hypoglycemic event and syncope, tropon peaked at 1, trending down and asymptomatic. Cr 1.0 EF 25-30% AC vdb. Angiomax gtt 0.25 mg/kg/hr.

I: Bivalurudin (plus clopidogrel plus ASA plus PCI – percutaneous coronary intervention).

C: Heparin plus (clopidogrel plus ASA plus PCI).

The Search:

1 Antithrombins/ or Recombinant Proteins/ or Angina Pectoris/ or Middle Aged/ or Hirudins/ or Hirudin Therapy/ or Anticoagulants/ or Angioplasty, Transluminal, Percutaneous Coronary/ or Peptide Fragments/ or bivalirudin.mp. 2846541

2 Heparin Antagonists/ or Heparin Lyase/ or Heparin/ or Heparin, Low-Molecular-Weight/ or Heparin Cofactor II/ or heparin.mp. 69761

3 (MI or ACS).mp. [mp=title, original title, abstract, name of substance word, subject heading word] 22291

4 1 and 3 and 2 539

5 limit 4 to (english language and full text and humans) 87

Article: N Engl J Med. 2008 Aug 14;359(7):688-96. **Bivalirudin versus unfractionated heparin during percutaneous coronary intervention. Kastrati A, Neumann FJ, Mehilli J, Byrne RA, Iijima R, Büttner HJ, Khattab AA, Schulz S, Blankenship JC, Pache J, Minners J, Seyfarth M, Graf I, Skelding KA, Dirschinger J, Richardt G, Berger PB, Schömig A; ISAR-REACT 3 Trial Investigators.**

Locations:

Munich (2), Bad Krozingen, Bad Segeberg, Germany

Inclusion Criteria:

- Pts with stable or unstable angina
- With normal levels of troponin T and creatine kinase MB
- Older than 18 years of age to undergo PCI
- 600-mg dose of clopidogrel loading at least 2 hrs prior to PCI (according to the PCI guidelines)
- Informed, written consent

Exclusion Criteria:

- Recent ST-elevation myocardial infarction within the last 48 hours
- Cardiogenic shock
- ACS and positive biomarkers (Troponin T > 0.03 µg/L)

- Malignancies or other comorbid conditions (for example severe liver, renal and pancreatic disease) with life expectancy less than one year or that may result in protocol non-compliance
- Active bleeding; bleeding diathesis
- History of gastrointestinal or genitourinary bleeding within the last 6 weeks
- Presence of diseases which have a high probability of vascular lesions and subsequent bleeding such as active gastric ulcer or active ulcerous colitis
- Recent trauma or major surgery in the last month
- Ophthalmic surgery or brain surgery in the last month
- Retinopathies or vitreous body bleeding in the last month
- History of intracranial bleeding or structural abnormalities (for example aneurysm of cerebral arteries)
- Suspected aortic dissection; pericarditis and subacute bacterial endocarditis
- Patient's refusal to blood transfusion
- Oral anticoagulation therapy with coumarin derivative within the last 7 days
- Treatment with UFH within 6 hours or low-molecular weight heparin within 8 hours before randomization
- Treatment with bivalirudin within 24 hours before randomization
- Severe uncontrolled hypertension >180/110 mmHg unresponsive to therapy
- Planned staged PCI procedure within 30 days from index procedure or prior PCI within the last 30 days
- Relevant hematologic deviations: hemoglobin < 100 g/L; platelet count < 100 x 10⁹ /L
- Glomerular filtration rate (GFR) < 30 ml/min or serum creatinine > 30 mg/L or dependence on renal dialysis
- Known allergy to the study medications: aspirin, clopidogrel, UFH, bivalirudin; stainless steel; true anaphylaxis after prior exposure to contrast media
- Known heparin-induced thrombocytopenia (Typ II)
- Previous enrollment in this trial
- Pregnancy (present, suspected or planned) or positive pregnancy test
- Spinal, peridural and epidural anesthesia
- Patient's inability to fully cooperate with the study protocol

Both groups: All patients who were enrolled in the trial received 600 mg of clopidogrel at least 2 hours before the PCI procedure. They also received 325 to 500 mg of aspirin.

Coronary stenting with either bare-metal or drug-eluting stents, according to the choice of the physician, was the preferred method of PCI. Vascular-access closure devices were used in 10% of the patients. Sheaths were removed and manual compression was applied as soon as the activated partial-thromboplastin time fell below 50 seconds. Postprocedural therapy included aspirin (80 to 325 mg per day indefinitely), clopidogrel (75 to 150 mg per day until discharge but for no longer than 3 days, followed by 75 mg per day for at least 1 month, in patients with bare-metal stents, or 6 months, in patients with drug-eluting stents), as well as all other cardiac medications that were recommended by the patients' physicians.

Double-blinding was achieved by using identical vials for the study drugs in the two groups. At one center, where 42 patients were enrolled, an initial dose of 100 U of heparin per kilogram was given and a monitor of activated clotting time who was unaware of the treatment assignments administered additional boluses of heparin or placebo if the activated clotting time was less than 250 seconds. All caregivers were unaware of the values for activated clotting time.

Arms	Assigned Interventions
Experimental n = 2289	Drug: Bivalirudin bivalirudin to be administered as an intravenous bolus of 0.75 mg/kg prior to the start of the intervention, followed by infusion of 1.75 mg/kg per hour for the duration of the procedure.
Active Comparator n = 2281	Drug: Un-fractionated heparin UFH is given as an intravenous bolus of 140 units/kg followed by infusion of placebo 1.75 mg/kg per hour for the duration of the procedure.

Primary Outcome Measures:

- Composite rate of death, myocardial infarction (MI), urgent target vessel revascularization (TVR) within 30 days or in-hospital major bleeding

Secondary Outcome Measures:

- Composite rate of death, MI or urgent TVR within 30 days
- Composite rate of death, MI or TVR at 1 year

Validity: Was the assignment of pts to treatments **randomized**?: Yes

Were all pts who entered the trial properly **accounted for** and attributed at its conclusion?: Yes

Was **follow up** completed?: Yes

Were pts **analyzed in the groups** to which they were randomized?: Yes

Were pts, health workers, and study personnel **“blind”** to treatment?: Yes

Were the **groups similar at the start** of the trial: Yes

Aside from the experimental intervention, were the **groups treated equally**?: Yes.

O/Results: The incidence of the primary end point was 8.3% (190 patients) in the bivalirudin group as compared with 8.7% (199 patients) in the unfractionated-heparin group (relative risk, 0.94; 95% confidence interval [CI], 0.77 to 1.15; P=0.57). The secondary end point occurred in 134 patients (5.9%) in the bivalirudin group and 115 patients (5.0%) in the unfractionated-heparin group (relative risk, 1.16; 95% CI, 0.91 to 1.49; P=0.23). The incidence of major bleeding was 3.1% (70 patients) in the bivalirudin group and 4.6% (104 patients) in the unfractionated-heparin group (relative risk, 0.66; 95% CI, 0.49 to 0.90; P=0.008).

Table 3. Primary Quadruple End Point, Secondary Triple End Point, and Their Components.

Event	Bivalirudin Group (N = 2289)	Unfractionated-Heparin Group (N = 2281)	Relative Risk (95% CI)
	no. (%)		
Death, myocardial infarction, urgent target-vessel revascularization, or major bleeding	190 (8.3)	199 (8.7)	0.94 (0.77–1.15)
Death, myocardial infarction, or urgent target-vessel revascularization	134 (5.9)	115 (5.0)	1.16 (0.91–1.49)
Death	3 (0.1)	4 (0.2)	
Myocardial infarction	128 (5.6)	110 (4.8)	
Q wave	14 (0.6)	9 (0.4)	
Urgent target-vessel revascularization	19 (0.8)	17 (0.7)	
Major bleeding*	70 (3.1)	104 (4.6)	0.66 (0.49–0.90)
Intracranial bleeding	1 (0.04)	2 (0.1)	
Retroperitoneal bleeding	4 (0.2)	3 (0.1)	
Hemoglobin decrease ≥ 3 g/dl with overt source	38 (1.7)	70 (3.1)	
Hemoglobin decrease ≥ 4 g/dl without overt source	21 (0.9)	22 (1.0)	
Blood transfusion	25 (1.1)	32 (1.4)	
Bleeding according to the TIMI definition [†]			
Major	12 (0.5)	24 (1.1)	
Minor	29 (1.3)	51 (2.2)	

* The components of major bleeding are listed hierarchically according to severity. The components do not sum because patients who had more than one component were counted as having only the most severe component, except in the case of blood transfusion, for which all instances were recorded.

[†] TIMI denotes Thrombolysis in Myocardial Infarction.

Back to the patient: This pt did not fit the inclusion criteria for this study (Trop to 1.0 at presentation), but was treated with angiomax and did undergo left heart cath 9/23/08. She was given Angiomax despite not fitting the study inclusion criteria b/c although Angiomax “does not confer a net clinical benefit in patients with stable and unstable angina who underwent PCI after pretreatment with clopidogrel, (i.e., it did not reduce the incidence of the composite end point of death, myocardial infarction, urgent target-vessel revascularization, or major bleeding) as compared with unfractionated heparin, it did significantly reduce the incidence of major bleeding,” which has prognostic value in terms of one year mortality for pts undergoing PCI (Ndrepepa G, Berger PB, Mehilli J, et al. Periprocedural bleeding and 1-year outcome after percutaneous coronary interventions: appropriateness of including bleeding as a component of a quadruple end point. J Am Coll Cardiol 2008;51:690-697). It is unclear to what extent Angiomax confers benefit in ACS pts not undergoing PCI.

APPENDIX – MECHANISMS/DRUG CLASS

Abciximab: Ig Fab fragments that blocks glycoprotein IIb/IIIa receptor on platelet membranes.

Eptifibatid (Integrilin): reversible, selective platelet glycoprotein IIb/IIIa receptor blockade.

Heparin: activates enzyme inhibitor antithrombin (AT), which then inactivates thrombin/other proteases, incl factor Xa.

Bivalirudin (Angiomax): reversible direct thrombin inhibitor; short-acting/good controllability.

Clopidogrel: irreversible platelet P2Y₁₂ (adenosine diphosphate – ADP) receptor blockade inhibiting glycoprotein IIb/IIIa pathway (cross-linking of platelets by fibrin).

ASA: irreversible inactivation of the COX enzyme and thus prostaglandin and thromboxane synthesis; irreversibly blocks the formation of TXA₂ in platelets with the prostaglandin I₂ synthesis being little affected at 40mg po daily.

<http://courses.ahc.umn.edu/pharmacy/5822/relevantclinicalstudies.html>