

# Clinical trials of bivalirudin

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## 1 acute myocardial infarction

Trial	Treatments	Patients	Trials design and methods
<b>bivalirudin vs heparin</b>			
<b>HERO , 1997</b> n=272/140 follow-up: 35 days	Bivalirudin 0.1250.250 mg/kg bolus; 0.1250.500 mg /kg/min infusion for 72h versus UFH 5000 IU bolus; 10001200 IU/h infusion	AMI (patients presenting within 12 hours with ST-segment elevation)	Parallel groups double blind

More details and results :

- antithrombotics for acute myocardial infarction in all type of patients at <http://www.trialresultscenter.org/go-Q36>

## References

### HERO, 1997:

White HD, Aylward PE, Frey MJ, Adgey AA, Nair R, Hillis WS, Shalev Y, Brown MA, French JK, Collins R, Maraganore J, Adelman B Randomized, double-blind comparison of hirulog versus heparin in patients receiving streptokinase and aspirin for acute myocardial infarction (HERO). Hirulog Early Reperfusion/Occlusion (HERO) Trial Investigators. Circulation 1997 Oct 7;96:2155-61 [9337184]

## 2 acute coronary syndrome

Trial	Treatments	Patients	Trials design and methods
<b>bivalirudin vs heparin + GP2b3a inhibitors</b>			
<b>ACUTY (biva alone vs hep+aGP2b3a) , 2006</b> [NCT00093158] n=4612/4603 follow-up: 30 days	bivalirudin alone versus unfractionated heparin or enoxaparin plus a glycoprotein IIb/IIIa inhibitor	in patients with moderate- or high-risk acute coronary syndromes who were undergoing an early invasive strategy.	Parallel groups double blind 17 countries worldwide

continued...

Trial	Treatments	Patients	Trials design and methods
ACUITY (sub groups PCI, bivalirudin alone) import , 2007 n=2619/2561 follow-up: 30 days	bivalirudin alone versus heparin (either unfractionated or enoxaparin) plus glycoprotein IIb/IIIa inhibitors	patients with moderate and high-risk acute coronary syndromes undergoing percutaneous coronary intervention after angiography (sub group).	Factorial plan open
<b>bivalirudin + GP2b3a inhibitors vs heparin + GP2b3a inhibitors</b>			
ACUITY (biva+aGP2b3a vs hep+aGP2b3a) , 2006 [NCT00093158] n=4604/4603 follow-up: 30 days	bivalirudin plus a glycoprotein IIb/IIIa inhibitor versus unfractionated heparin or enoxaparin plus a glycoprotein IIb/IIIa inhibitor	in patients with moderate- or high-risk acute coronary syndromes who were undergoing an early invasive strategy.	double blind 17 countries worldwide
ACUITY (sub groups PCI, bivalirudin +aGP2b3a) import , 2007 n=2609/2561 follow-up: 30 days	bivalirudin + versus heparin (either unfractionated or enoxaparin) plus glycoprotein IIb/IIIa inhibitors	patients with moderate and high-risk acute coronary syndromes undergoing percutaneous coronary intervention after angiography.	open
<b>bivalirudin vs eptifibatide + heparin</b>			
PROTECT-TIMI 30 , 2006 [NCT00250471] n=284/573 follow-up: hospital stay	bivalirudin alone versus eptifibatide plus either unfractionated heparin or enoxaparin	non ST elevation ACS patients undergoing PCI	Parallel groups open International
<b>bivalirudin vs heparin</b>			
HERO , 1997 n=272/140 follow-up: 35 days	Bivalirudin 0.1250.250 mg/kg bolus; 0.1250.500 mg /kg/min infusion for 72h versus UFH 5000 IU bolus; 10001200 IU/h infusion	AMI (patients presenting within 12 hours with ST-segment elevation)	Parallel groups double blind
BAT (Bittl) , 1995 n=2059/2039 follow-up: 6 months	Bivalirudin 1.0 mg/kg bolus; 2.5 mg /kg/h for 4 h, then 0.2 mg /kg/h infusion for 24h versus UFH 175 IU/kg bolus; 15 IU mg /kg/h infusion	patients undergoing angioplasty for unstable or postinfarction angina	Parallel groups double blind North America and Europe

More details and results :

- antithrombotics for acute coronary syndrome in all type of patients at <http://www.trialresultscenter.org/go-Q24>
- antithrombotics for acute coronary syndrome in patients managed with an early invasive strategy at <http://www.trialresultscenter.org/go-Q347>

- antithrombotics for acute coronary syndrome in PCI sub group at <http://www.trialresultscenter.org/go-Q348>

## References

### **ACUITY (biva alone vs hep+aGP2b3a), 2006:**

Stone GW, McLaurin BT, Cox DA, Bertrand ME, Lincoff AM, Moses JW, White HD, Pocock SJ, Ware JH, Feit F, Colombo A, Aylward PE, Cequier AR, Darius H, Desmet W, Ebrahimi R, Hamon M, Rasmussen LH, Rupprecht HJ, Hoekstra J, Mehran R, Ohman EM Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006 Nov 23;355:2203-16 [[17124018](#)]

Singh S, Molnar J, Arora R Efficacy and safety of bivalirudin versus heparins in reduction of cardiac outcomes in acute coronary syndrome and percutaneous coronary interventions. *J Cardiovasc Pharmacol Ther* 2007;12:283-91 [[18172222](#)]

Stone GW, Ware JH, Bertrand ME, Lincoff AM, Moses JW, Ohman EM, White HD, Feit F, Colombo A, McLaurin BT, Cox DA, Manoukian SV, Fahy M, Clayton TC, Mehran R, Pocock SJ Antithrombotic strategies in patients with acute coronary syndromes undergoing early invasive management: one-year results from the ACUITY trial. *JAMA* 2007 Dec 5;298:2497-506 [[18056903](#)]

### **ACUITY (sub groups PCI, bivalirudin alone) import, 2007:**

Stone GW, Ware JH, Bertrand ME, Lincoff AM, Moses JW, Ohman EM, White HD, Feit F, Colombo A, McLaurin BT, Cox DA, Manoukian SV, Fahy M, Clayton TC, Mehran R, Pocock SJ, , Antithrombotic strategies in patients with acute coronary syndromes undergoing early invasive management: one-year results from the ACUITY trial. *JAMA* 2007;298:2497-506. [[18056903](#)] [10.1001/jama.298.21.2497](#)

Stone GW, White HD, Ohman EM, Bertrand ME, Lincoff AM, McLaurin BT, Cox DA, Pocock SJ, Ware JH, Feit F, Colombo A, Manoukian SV, Lansky AJ, Mehran R, Moses JW, , Bivalirudin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a subgroup analysis from the Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial. *Lancet* 2007;369:907-19. [[17368152](#)] [10.1016/S0140-6736\(07\)60450-4](#)

Stone GW, Bertrand M, Colombo A, Dangas G, Farkouh ME, Feit F, Lansky AJ, Lincoff AM, Mehran R, Moses JW, Ohman M, White HD, Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial: study design and rationale. *Am Heart J* 2004;148:764-75. [[15523305](#)] [10.1016/j.ahj.2004.04.036](#)

### **ACUITY (biva+aGP2b3a vs hep+aGP2b3a), 2006:**

Stone GW, Ware JH, Bertrand ME, Lincoff AM, Moses JW, Ohman EM, White HD, Feit F, Colombo A, McLaurin BT, Cox DA, Manoukian SV, Fahy M, Clayton TC, Mehran R, Pocock SJ Antithrombotic strategies in patients with acute coronary syndromes undergoing early invasive management: one-year results from the ACUITY trial. *JAMA* 2007 Dec 5;298:2497-506 [[18056903](#)]

### **ACUITY (sub groups PCI, bivalirudin +aGP2b3a) import, 2007:**

Stone GW, White HD, Ohman EM, Bertrand ME, Lincoff AM, McLaurin BT, Cox DA, Pocock SJ, Ware JH, Feit F, Colombo A, Manoukian SV, Lansky AJ, Mehran R, Moses JW, , Bivalirudin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a subgroup analysis from the Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial. *Lancet* 2007;369:907-19. [[17368152](#)] [10.1016/S0140-6736\(07\)60450-4](#)

### **PROTECT-TIMI 30, 2006:**

Gibson CM, Morrow DA, Murphy SA, Palabrica TM, Jennings LK, Stone PH, Lui HH, Bulle T, Lakkis N, Kovach R, Cohen DJ, Fish P, McCabe CH, Braunwald E A randomized trial to evaluate the relative protection against post-percutaneous coronary intervention microvascular dysfunction, ischemia, and inflammation among antiplatelet and antithrombotic agents: the PROTECT-TIMI-30 trial. *J Am Coll Cardiol* 2006;47:2364-73 [[16781360](#)]

### **HERO, 1997:**

White HD, Aylward PE, Frey MJ, Adgey AA, Nair R, Hillis WS, Shalev Y, Brown MA, French JK, Collins R, Maraganore J, Adelman B Randomized, double-blind comparison of hirulog versus heparin in patients receiving streptokinase and aspirin for acute myocardial infarction (HERO). *Hirulog Early Reperfusion/Occlusion*

(HERO) Trial Investigators. Circulation 1997 Oct 7;96:2155-61 [9337184]

### BAT (Bittl), 1995:

Bittl JA, Strony J, Brinker JA, Ahmed WH, Meckel CR, Chaitman BR, Maraganore J, Deutsch E, Adelman B Treatment with bivalirudin (Hirulog) as compared with heparin during coronary angioplasty for unstable or postinfarction angina. Hirulog Angioplasty Study Investigators. N Engl J Med 1995 Sep 21;333:764-9 [7643883]

## 3 percutaneous coronary intervention

Trial	Treatments	Patients	Trials design and methods
<b>bivalirudin vs heparin + GP2b3a inhibitors</b>			
<b>ACUITY (Stone) (bivalirudin alone) , 2006</b> [NCT00093158] n=9216/4603 follow-up: 30 days	bivalirudin alone versus unfractionated heparin or enoxaparin plus a glycoprotein IIb/IIIa inhibitor	patients with acute coronary syndromes	Parallel groups open
<b>HORIZONS-AMI (Stone) , 2008</b> [NCT00433966] n=1800/1802 follow-up: 30 days	Bivalirudin versus Heparin plus GP IIb/IIIa inhibitor	patients with ST-segment elevation myocardial infarction who presented within 12 hours after the onset of symptoms and who were undergoing primary PCI	Parallel groups open 11 countries
<b>REPLACE-2 , 2003</b> n=2994/3008 follow-up: 30 days	bivalirudin, with glycoprotein IIb/IIIa (Gp IIb/IIIa) inhibition on a provisional basis for complications during PCI versus heparin plus planned Gp IIb/IIIa blockade	patients undergoing urgent or elective PCI	Parallel groups double blind 9 countries
<b>bivalirudin + eptifibatide vs heparin + GP2b3a inhibitors</b>			
<b>Kleiman , 2002</b> n=NA follow-up:	bivalirudin + eptifibatide versus heparin + eptifibatide	patients who underwent elective percutaneous coronary intervention	Parallel groups open
<b>bivalirudin vs UFH</b>			
<b>ARMYDA BIVALVE</b> n=140 follow-up:	bivalirudin (0.75 mg/kg bolus followed by 1.75 mg/kg per hour during the procedure) versus unfractionated heparin (75 IU/kg)	patients at high bleeding risk (over 75 years of age, diabetes, reduced renal function) scheduled for PCI	Parallel groups
<b>BAT (Bittl) , 1995</b> n=2059/2039 follow-up: hospital stay	bivalirudin immediately before angioplasty. versus heparin immediately before angioplasty	patients undergoing urgent angioplasty for unstable or postinfarction angina	Parallel groups double blind US

continued...

Trial	Treatments	Patients	Trials design and methods
<b>ISAR-REACT 3 , 2008</b> [NCT00262054] n=2289/2281 follow-up: 30 days (mean)	UFH bolus of 140 U/kg versus bivalirudin (bolus of 0.75 mg/kg, followed by infusion of 1.75 mg/kg/hr)	troponin-negative patients undergoing PCI	Parallel groups double blind
<b>REPLACE-1 , 2004</b> n=532/524 follow-up: hospital stay (48h min)	bivalirudin (0.75 mg/kg bolus, 1.75 mg/kg/h infusion during the procedure versus heparin (70 U/kg initial bolus) adjusted to ACT of 200 to 300s	patients undergoing elective or urgent revascularization	Parallel groups US
<b>bivalirudin vs UFH plus tirofiban</b>			
<b>NAPLES (Tavano) , 2009</b> n=167/168 follow-up: 30 days	bivalirudin monotherapy versus unfractionated heparin plus tirofiban	patients with diabetes mellitus undergoing elective percutaneous coronary intervention	Parallel groups open Italy
<b>Prasugrel and Bivalirudin vs Clopidogrel and Heparin</b>			
<b>BRAVE-4 ongoing</b> [NCT00976092] n=NA follow-up:	Prasugrel + Bivalirudin versus Clopidogrel + Heparin	STEMI patients undergoing PPCI	

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More details and results :

- antithrombotics for percutaneous coronary intervention in all type of patients at <http://www.trialresultscenter.org/go-Q63>
- anticoagulant for percutaneous coronary intervention in all type of patients at <http://www.trialresultscenter.org/go-Q388>

## References

### **ACUITY (Stone) (bivalirudin alone), 2006:**

Stone GW, McLaurin BT, Cox DA, Bertrand ME, Lincoff AM, Moses JW, White HD, Pocock SJ, Ware JH, Feit F, Colombo A, Aylward PE, Cequier AR, Darius H, Desmet W, Ebrahimi R, Hamon M, Rasmussen LH, Rupprecht HJ, Hoekstra J, Mehran R, Ohman EM, , Bivalirudin for patients with acute coronary syndromes. N Engl J Med 2006;355:2203-16. [17124018] [10.1056/NEJMoa062437](https://doi.org/10.1056/NEJMoa062437)

### **HORIZONS-AMI (Stone), 2008:**

Mehran R, Brodie B, Cox DA, Grines CL, Rutherford B, Bhatt DL, Dangas G, Feit F, Ohman EM, Parise H, Fahy M, Lansky AJ, Stone GW, The Harmonizing Outcomes with RevascularizatiON and Stents in Acute Myocardial Infarction (HORIZONS-AMI) Trial: study design and rationale. Am Heart J 2008;156:44-56. [18585496] [10.1016/j.ahj.2008.02.008](https://doi.org/10.1016/j.ahj.2008.02.008)

Stone GW, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, Kornowski R, Hartmann F, Gersh BJ, Pocock SJ, Dangas G, Wong SC, Kirtane AJ, Parise H, Mehran R Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008 May 22;358:2218-30 [18499566]

Stone GW, Witzentichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, Kornowski R, Hartmann F, Gersh BJ, Pocock SJ, Dangas G, Wong SC, Fahy M, Parise H, Mehran R Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction (HORIZONS-AMI): final 3-year results from a multicentre, randomised controlled trial. *Lancet* 2011 Jun 25;377:2193-2204 [[21665265](#)] [10.1016/S0140-6736\(11\)60764-2](#)

#### **REPLACE-2, 2003:**

Gibson CM, Ten Y, Murphy SA, Ciaglio LN, Southard MC, Lincoff AM, Waksman R, Association of prerandomization anticoagulant switching with bleeding in the setting of percutaneous coronary intervention (A REPLACE-2 analysis). *Am J Cardiol* 2007;99:1687-90. [[17560876](#)] [10.1016/j.amjcard.2007.01.053](#)

Cohen DJ, Lincoff AM, Lavelle TA, Chen HL, Bakhai A, Berezin RH, Jackman D, Sarembock IJ, Topol EJ, Economic evaluation of bivalirudin with provisional glycoprotein IIB/IIIA inhibition versus heparin with routine glycoprotein IIB/IIIA inhibition for percutaneous coronary intervention: results from the REPLACE-2 trial. *J Am Coll Cardiol* 2004;44:1792-800. [[15519009](#)] [10.1016/j.jacc.2004.05.085](#)

Lincoff AM, Kleiman NS, Kereiakes DJ, Feit F, Bittl JA, Jackman JD, Sarembock IJ, Cohen DJ, Spriggs D, Ebrahimi R, Keren G, Carr J, Cohen EA, Betriu A, Desmet W, Rutsch W, Wilcox RG, de Feyter PJ, Vahanian A, Topol EJ, , Long-term efficacy of bivalirudin and provisional glycoprotein IIb/IIIa blockade vs heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary revascularization: REPLACE-2 randomized trial. *JAMA* 2004;292:696-703. [[15304466](#)] [10.1001/jama.292.6.696](#)

Lincoff AM, Bittl JA, Harrington RA, Feit F, Kleiman NS, Jackman JD, Sarembock IJ, Cohen DJ, Spriggs D, Ebrahimi R, Keren G, Carr J, Cohen EA, Betriu A, Desmet W, Kereiakes DJ, Rutsch W, Wilcox RG, de Feyter PJ, Vahanian A, Topol EJ Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA* 2003 Feb 19;289:853-63 [[12588269](#)]

#### **Kleiman, 2002:**

Kleiman NS, Klem J, Fernandes LS, Rubin H, Challa S, Solomon S, Maresh K, Arora U, Klem E, Buerger J, Mathew S, Browning A, DeLao T, Pharmacodynamic profile of the direct thrombin antagonist bivalirudin given in combination with the glycoprotein IIb/IIIa antagonist eptifibatid. *Am Heart J* 2002;143:585-93. [[11923794](#)]

#### **ARMYDA BIVALVE, :**

#### **BAT (Bittl), 1995:**

Bittl JA, Feit F, A randomized comparison of bivalirudin and heparin in patients undergoing coronary angioplasty for postinfarction angina. Hirulog Angioplasty Study Investigators. *Am J Cardiol* 1998;82:43P-49P. [[9809891](#)]

Shah PB, Ahmed WH, Ganz P, Bittl JA, Bivalirudin compared with heparin during coronary angioplasty for thrombus-containing lesions. *J Am Coll Cardiol* 1997;30:1264-9. [[9350925](#)]

Bittl JA, Strony J, Brinker JA, Ahmed WH, Meckel CR, Chaitman BR, Maraganore J, Deutsch E, Adelman B, Treatment with bivalirudin (Hirulog) as compared with heparin during coronary angioplasty for unstable or postinfarction angina. Hirulog Angioplasty Study Investigators. *N Engl J Med* 1995;333:764-9. [[7643883](#)]

Bittl JA, Comparative safety profiles of hirulog and heparin in patients undergoing coronary angioplasty. The Hirulog Angioplasty Study Investigators. *Am Heart J* 1995;130:658-65. [[7668214](#)]

Bittl JA, Chaitman BR, Feit F, Kimball W, Topol EJ Bivalirudin versus heparin during coronary angioplasty for unstable or postinfarction angina: Final report reanalysis of the Bivalirudin Angioplasty Study. *Am Heart J* 2001;142:952-9 [[11717596](#)]

#### **ISAR-REACT 3, 2008:**

Kastrati A, Neumann FJ, Mehilli J, Byrne RA, Iijima R, Bttner HJ, Khat tab AA, Schulz S, Blankenship JC, Pache J, Minners J, Seyfarth M, Graf I, Skelding KA, Dirschinger J, Richardt G, Berger PB, Schmig A Bivalirudin versus Unfractionated Heparin during Percutaneous Coronary Intervention. *N Engl J Med* 2008 Aug 14;359:688-696 [[18703471](#)]

**REPLACE-1, 2004:**

Lincoff AM, Bittl JA, Kleiman NS, Sarembock IJ, Jackman JD, Mehta S, Tannenbaum MA, Niederman AL, Bachinsky WB, Tift-Mann J, Parker HG, Kereiakes DJ, Harrington RA, Feit F, Maierson ES, Chew DP, Topol EJ, , Comparison of bivalirudin versus heparin during percutaneous coronary intervention (the Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events [REPLACE]-1 trial). Am J Cardiol 2004;93:1092-6. [[15110198](#)] [10.1016/j.amjcard.2004.01.033](#)

**NAPLES (Tavano), 2009:**

Tavano D, Visconti G, D'Andrea D, Focaccio A, Golia B, Librera M, Caccavale M, Ricciarelli B, Briguori C Comparison of bivalirudin monotherapy versus unfractionated heparin plus tirofiban in patients with diabetes mellitus undergoing elective percutaneous coronary intervention. Am J Cardiol 2009;104:1222-8 [[19840566](#)]

**BRAVE-4, :**

ongoing trial NCT00976092

Entry terms: Hirulog-1 Hirulog Angiomax