

What is the best anticoagulant therapy during primary percutaneous coronary intervention for acute myocardial infarction?

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KEY WORDS

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ABSTRACT

Both ST-segment elevation myocardial infarction and percutaneous coronary intervention (PCI) are associated with a highly prothrombotic state, and thrombin plays a critical role during occlusive clot generation and subsequent occurrence of an ischemic event. Therefore, a strategy of anticoagulation plus dual antiplatelet therapy has been regarded as de facto standard therapy during primary PCI (pPCI). Recently, there has been great controversy surrounding the role of bivalirudin versus unfractionated heparin in pPCI. Earlier, the results of the HORIZONS-AMI trial, particularly those regarding the long-lasting mortality benefit, provided a strong rationale for recommending bivalirudin therapy in pPCI. However, the mortality benefit of bivalirudin observed in HORIZONS-AMI has not been repeated in more contemporary studies or demonstrated in recent meta-analyses. The current report will provide a concise review of the controversy surrounding the optimal anticoagulant therapy for pPCI. Recent evidence suggests that unfractionated heparin deserves strong reconsideration despite the reports of pharmacologic weaknesses, particularly when used with a strategy of selective glycoprotein IIb/IIIa therapy, and it appears that a strategy of bivalirudin therapy in pPCI should be reserved for patients at high bleeding risk.

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Introduction Generation of a stable and occlusive intracoronary thrombus at the site of atherosclerotic plaque rupture or erosion is the hallmark feature of ST-segment elevation myocardial infarction (STEMI). Thrombotic occlusion of a major epicardial coronary artery and distal embolization of components released from the plaque and thrombus result in impaired myocardial perfusion.^{1,2} Histopathological evaluation, proteomics, and the gene expression profile of coronary thrombi aspirated during primary percutaneous coronary intervention (pPCI) revealed that platelets, fibrin, erythrocytes, atheroma, and inflammatory cells are the major components of the thrombus.³⁻⁸ It has been suggested that the cellular components of the thrombus are dependent on the ischemic time where the platelet content correlates inversely and the fibrin content directly with the time from symptom onset to pPCI. The initial “fresh” white thrombus consists mainly of platelets.^{7,8} Blood stasis at the occlusion site

stimulates the coagulation pathway and subsequent fibrin accumulation entraps a large number of erythrocytes and inflammatory cells to form a “red thrombus” and stabilize the occlusive thrombus.^{8,9} The latter “red thrombus” propagates proximally and distally after the onset of STEMI. Thus, both platelet activation and aggregation and coagulation are critical in the development of an occlusive thrombus, and antithrombotic strategies that target both pathways are essential during treatment of STEMI.

In patients with STEMI, pPCI is the preferred reperfusion strategy. The major goal of pPCI is the achievement of infarct-related artery patency and the restoration of myocardial perfusion, which are critically dependent on the extent of the thrombus burden. The optimal antithrombotic strategy remains elusive. Despite recent significant advances in pPCI techniques and novel pharmacologic therapy strategies, a substantial percentage of patients treated with pPCI show

TABLE Randomized clinical trials of bivalirudin versus heparin therapies

	Randomization	N	Bivalirudin infusion	GPI bailout, %	Access site, %	30-day primary outcome, %	Mortality	ST	Bleeding
HORIZONS-AMI (2008)	bivalirudin (0.75 mg/kg bolus + 1.75 mg/kg/h infusion) + clopidogrel (95.7%), ticlopidine (0.4%)	1800	procedure duration (continued at physician's discretion)	7.2	femoral	NACE = 9.2 vs 12.1 RR = 0.76, P = 0.005	all cause = 2.1% vs 3.1%, RR = 0.66, P = 0.047	definite = 2.2% vs 1.4%, P = 0.09 Acute = 1.3% vs 0.3%, P < 0.001	protocol-defined non-CABG major 4.9% vs 8.3% RR = 0.60, P < 0.0001 TIMI Major 3.1 vs 5.0, P = 0.002
	UFH (60 IU body weight targeted at ACT 200–250 s) + GPI (abciximab 0.25 mg/kg + 0.125 µg/kg/min infusion for 12 h (52%), or double dose eptifibatide 180 µg/kg + 2.0 µg/kg/min infusion for 12–18 h (46%)) + clopidogrel (95.1%), ticlopidine (0.4%)	1802	–	NA	femoral	MACE 5.5 vs 5.5	cardiac = 1.8% vs 2.9%, RR = 0.62, P = 0.03		
BRAVE -4 (2014)	bivalirudin (0.75 mg/kg bolus + 1.75 mg/kg/h infusion) + prasugrel (95%)	271	procedure duration	3.0		NACE = 15.6 vs 14.5, RR = 1.06, P = 0.68.	all cause = 2.6 vs 2.5, RR = 1.02, P = 0.85.	definite = 1.1 vs 1.5, RR = 0.77, P = 0.98	TIMI major 2.6 vs 2.9 RR = 0.89, P = 0.97
	UFH (70–100 IU/kg) + clopidogrel (90%)	277	–	6.1		MACE 4.8 vs 5.5, RR = 0.89, P = 0.89			HORIZON-AMI definition 14.1 vs 12.0, RR = 1.18, P = 0.54
EUROMAX (2013)	bivalirudin (0.75 mg/kg bolus + 1.75 mg/kg/h infusion) + clopidogrel (50%), prasugrel (30.8%), ticagrelor (19.2%)	1089	procedure duration continued for 4 h	7.9	femoral = 52 radial = 48	death or non-CABG major bleeding 5.1 vs 8.5 RR = 0.60, P = 0.001	all cause = 2.5 vs 3.0, RR = .83, P = .48	definite = 1.6 vs 0.5, RR = 2.89, P = 0.02	protocol-defined non-CABG major 2.6% vs 6.0% RR = 0.43, P < 0.0001
	UFH (100 IU/kg bolus) + clopidogrel (50%) + GPI (69.1%) LMWH (0.5 mg/kg) + clopidogrel (51.5%), prasugrel (28.9%), ticagrelor (19.4%)	1109	–	25.4	femoral = 54 radial = 46	MACE 6.0 vs 5.5 RR = 1.09, P = 0.64 NACE 7.8 vs 10.6 RR = 0.73, P = 0.02	cardiac = 2.9 vs 3.1, RR = .96, P = 0.86	acute = 1.1 vs 0.2, RR = 6.11, P = 0.007	TIMI major 1.3 vs 2.1, P = 0.15

HEAT-PPCI (2014)	bivalirudin (0.75 mg/kg bolus + 1.75 mg/kg/h infusion) a rebolus of 0.3 mg/kg if ACT <225 s + clopidogrel (12%), prasugrel (27%), ticagrelor (61%)	905	procedure duration	13	femoral = 19 radial = 80	MACE = 8.7 vs 5.7 RR = 1.52, <i>P</i> = 0.01	all cause 5.1 vs 4.3, RR = 1.52, <i>P</i> = 0.01	definite 3.3 vs 0.7, RR = 4.5, <i>P</i> = 0.001 acute = 2.9 vs 0.9, RR = 3.26, <i>P</i> = 0.007	BARC 3–5 3.5 vs 3.1, RR = 1.15, <i>P</i> = 0.59
BRIGHT (2014)	UFH (70 IU/kg) before procedure + additional doses if ACT <200 s + clopidogrel (10%), prasugrel (27%), ticagrelor (61%) all antiplatelet agents before pPCI	907		15	femoral = 18 radial = 82				
STEMI+ NSTEMI	bivalirudin (0.75 mg/kg bolus + 1.75 mg/kg/h infusion) + clopidogrel (100%) a rebolus of 0.3 mg/kg if ACT <225 s UFH (100 IU/kg) + clopidogrel (100%) ACT goal = 250–300 s UFH (60 IU/kg) + tirofiban + clopidogrel (99.9%) ACT goal = 200–250 s	735 729	procedure duration (at least 30 min)	4.4 5.7	femoral = 22 radial = 78 femoral = 21 radial = 79 femoral = 22 radial = 78	MACE 5.0 vs 5.8 vs 4.9 <i>P</i> = 0.74 NACE 8.8 vs 13.2 vs 17.0 <i>P</i> <0.001	all cause = 1.8 vs 1.8 vs 2.1 cardiac 1.7 vs 1.8 vs 2.1	definite = 0.4 vs 0.7 vs 0.6 acute 0.3 vs 0.3 vs 0.3	BARC 3–5 0.5 vs 1.5 vs 2.1 <i>P</i> = 0.04

HORIZONS-AMI: NACE = combination of major bleeding or major adverse cardiovascular events, including death, reinfarction, target-vessel revascularization for ischemia, and stroke; major bleeding = intracranial or intraocular hemorrhage; bleeding at the access site, with a hematoma that was 5 cm or larger or that required intervention; a decrease in the hemoglobin level of 4 g/dl or more without an overt bleeding source of 3 g/dl or more with an overt bleeding source; reoperation for bleeding; or blood transfusion. **BRAVE 4 study:** NACE = composite endpoint of death, MI, unplanned revascularization of the infarct-related artery, stent thrombosis, stroke, or bleeding

EUROMAX trial: NACE = composite of major adverse cardiovascular events and non-CABG major bleeding, each of the components of the primary and principal secondary outcomes, ischemia-driven by the Academic Research Consortium, and a composite of reinfarction, ischemia-driven revascularization, or stent thrombosis. Protocol definition of major bleeding was bleeding unrelated to CABG surgery that included intracranial, retroperitoneal, or intraocular bleeding; access-site hemorrhage requiring radiological or surgical intervention; a reduction in the hemoglobin level of more than 4 g/dl (2.5 mmol/l) without an overt source of bleeding; a reduction in the hemoglobin level of more than 3 g/dl (1.8 mmol/l) with an overt source of bleeding; reintervention for bleeding; or use of any blood-product transfusion

HEAT-PCI: primary efficacy outcome = composite of all-cause mortality, cerebrovascular accident, reinfarction, or unplanned target lesion revascularization; primary safety outcome = incidence of major bleeding (type 3–5 as per Bleeding Academic Research Consortium definitions)

BRIGHT trial: primary endpoint = 30-day NACE, a composite of major adverse cardiac or cerebral events (all-cause death, reinfarction, ischemia-driven target vessel revascularization, or stroke) or bleeding

Abbreviations: ACT, activated clotting time; BARC, Bleeding Academic Research Consortium; CABG, coronary artery bypass grafting; GPI, glycoprotein IIb/IIIa inhibitors; MACE, major adverse clinical events; NA, not available; NACE, net adverse clinical events; pPCI, primary percutaneous coronary intervention; RR, relative risk; UFH, unfractionated heparin; TIMI, Thrombolysis in Myocardial Infarction

poor clinical outcomes. The latter have been attributed to periprocedural micro- and macroembolization.⁹ It has been reported that direct par-enteral factor IIa inhibition as compared with a strategy employing unfractionated heparin + glycoprotein IIb/IIIa inhibition (GPI) was associated with a reduction in mortality and less bleeding.^{10,11} It is also known that multiple ruptured or rupture-prone plaques coexist synchronously elsewhere in the coronary circulation in the presence of the culprit occlusive thrombus.¹² In light of this observation, a long-term strategy to attenuate coagulation with factor Xa (FXa) inhibitor on top of dual antiplatelet therapy with aspirin and a P2Y₁₂ inhibitor has been associated with positive outcomes in patients with recent acute coronary syndromes (ACS).¹³ The current report will provide a concise review of the controversy surrounding the optimal anticoagulant therapy for pPCI.

Anticoagulants Thrombin is a serine protease with one active site and two anion-binding exosites, I and II, adjacent to the active site. Exosite I is specific for fibrin(ogen) and protease activated receptors and is responsible for the sequestration of thrombin in fibrin clots, whereas FXI, FXIII, and antithrombin (AT) interact with exosite II, a glycosaminoglycan-binding site. The active site and exosites I and II are targets for anticoagulants.¹⁴⁻¹⁶

Unfractionated heparin (UFH) is an indirect thrombin inhibitor belonging to a family of highly sulfated polysaccharides. Pharmaceutical-grade heparin is mainly derived from porcine intestines or bovine lungs.¹⁷ Heparin simultaneously binds to both AT (a naturally occurring serine protease inhibitor) via its pentasaccharide sequence, and exosite II of thrombin, thereby significantly accelerating AT-mediated inhibition of thrombin. In the UFH/AT complex, UFH keeps thrombin in the proper steric configuration for AT to exert its action to block the active site of thrombin. Subsequently, thrombin cleaves the reactive center loop of AT to form a covalent thrombin/AT complex. Heparin then dissociates from this complex and is able to bind to additional AT molecules. Most of the anticoagulant activity of UFH is confined to the unique and high-affinity pentasaccharide sequence that is present in only one-third of the heparin chains, whereas heparin chains without the pentasaccharide sequence have minimal anticoagulant activity when administered at standard doses. In an AT-dependent fashion, heparin can also inactivate factors Xa, XII, XI, and IX, but the clinical relevance of the latter properties of heparin is uncertain. The heparin-AT complex is 10 times more potent in inhibiting thrombin as compared with inhibiting activated FXa. Heparin inhibits FXa by binding to AT alone, and its binding to FXa is not necessary.¹⁶ The anticoagulant property of UFH is widely variable due to 1) only about one-third of the administered heparin molecules have the pentasaccharide sequence

possessing the anticoagulant effect; 2) UFH variably binds to numerous plasma proteins in addition to AT; 3) UFH is neutralized by platelet factor released from activated platelets that may be relevant during thrombus generation at the site of plaque rupture where platelet factor 4 is generated in high local concentrations; and 4) UFH also binds to endothelial cells and macrophages where it is internalized and depolymerized. The latter pathway is attributed to the rapid clearance of heparin's major saturable proportion. Unsaturable heparin is cleared renally in a much slower fashion. Therefore, UFH administration requires close monitoring. UFH does not effectively inhibit fibrin-bound thrombin. Finally, UFH has been associated with platelet activation and thrombocytopenia.¹⁶

Low-molecular-weight heparin Low-molecular-weight heparins (LMWHs) are produced from UFH by chemical or enzymatic depolymerization. Due to variability in preparation methods, different formulations of LMWH are associated with different pharmacokinetic and anticoagulant properties.¹⁴⁻¹⁶ LMWHs have a reduced anticoagulant effect compared with UFH since only one-fifth of LMWHs possess the pentasaccharide sequence. The shortened chain length of LMWHs cannot effectively bind simultaneously to AT and thrombin. The short chain retains the capacity to promote FXa inhibition more effectively as compared with UFH, since the latter reaction does not require bridging. After its subcutaneous injection, LMWHs have bioavailability of nearly 90% and a more predictable dose-response relationship compared with UFH, owing to reduced binding to plasma proteins. LMWHs have longer half-life compared with UFH. Since LMWHs are cleared by the kidneys, their biological half-life is critically dependent on renal function.¹⁴⁻¹⁶

Bivalirudin The direct thrombin inhibitors (DTIs), bivalirudin, hirudin, and dabigatran, directly bind to thrombin. DTIs are associated with predictable anticoagulant effect, since they do not bind to plasma proteins. Furthermore, DTIs do not require AT and inhibit both fibrin-bound and soluble thrombin. Bivalirudin is a 20 amino acid synthetic polypeptide and is an analog of hirudin. Bivalirudin binds to both the active site and exosite I of thrombin, thereby competing with exosite I for fibrin binding and enhancing displacement of thrombin from fibrin. Following its binding to bivalirudin, thrombin cleaves the Pro-Arg bond within the amino terminal of bivalirudin, thereby allowing recovery of thrombin activity. Bivalirudin has a plasma half-life of 25 minutes after intravenous (IV) administration, and only 20% is cleared through the kidneys. It has been reported that bivalirudin can inhibit thrombin-induced platelet aggregation.¹⁴⁻¹⁶

Guideline recommendations for primary percutaneous coronary interventions **2012 European Society of Cardiology Guidelines for the management of acute myocardial infarction in patients with ST-segment elevation**¹

- bivalirudin (with the use of GP IIb/IIIa blocker restricted to bailout) (0.75 mg/kg IV bolus followed by IV infusion of 1.75 mg/kg/h for up to 4 h after the procedure as clinically warranted. Then a reduced infusion dose of 0.25 mg/kg/h may be continued for 4–12 h as clinically necessary) is recommended over UFH plus GPI (Class I, Level of Evidence B)
- enoxaparin (0.5-mg/kg IV bolus) may be preferred over UFH (Class IIb, Level of Evidence B)
- UFH with GPI (50–60-U/kg IV bolus) or without GPI (70–100-U/kg IV bolus) must be used in patients not receiving bivalirudin or enoxaparin (Class I, Level of Evidence C)
- no fondaparinux because of risk of catheter thrombosis (Class III, Level of Evidence B).

2013 American College of Cardiology Foundation/American Heart Association Guideline for the Management of ST-Elevation Myocardial Infarction²

- UFH: with GPI, 50- to 70-U/kg IV bolus to achieve therapeutic activated clotting time (ACT); without GPI, 70- to 100-U/kg bolus infusion to achieve therapeutic ACT (Class I, Level of Evidence C)
- bivalirudin (0.75-mg/kg IV bolus, then 1.75-mg/kg/h infusion with or without prior treatment with UFH. An additional bolus of 0.3 mg/kg may be given if needed) with or without prior treatment with UFH (Class I, Level of Evidence: B)
- in patients who are at high risk of bleeding, it is reasonable to use bivalirudin monotherapy in preference to the combination of UFH and a GPI (Class IIa, Level of Evidence: B)
- no fondaparinux because of risk of catheter thrombosis (Class III, Level of Evidence: B).

2014 European Society of Cardiology and European Association of Cardio-Thoracic Surgery Guidelines on myocardial revascularization¹⁸

- UFH with GPI (50–70-U/kg IV bolus) or without GPI (70–100-U/kg IV bolus) (Class I, Level of Evidence C)
- bivalirudin (0.75-mg/kg IV bolus followed by IV infusion of 1.75 mg/kg/h for up to 4 h after the procedure) (Class IIa, Level of Evidence A)
- enoxaparin (0.5-mg/kg IV bolus) (Class IIa, Level of Evidence B).

Clinical trials Randomized clinical trials comparing bivalirudin and heparin therapies are summarized in the [TABLE](#). Since both STEMI and PCI are associated with a highly prothrombotic state and thrombin plays a critical role during occlusive clot generation, heparins are regarded as de facto standard therapy during pPCI. Therefore, the safety and efficacy of UFH or LMWHs versus placebo have not been studied in randomized trials.

In an early meta-analysis of 16 studies comprising 7611 ACS patients treated with stents and thienopyridines, UFH plus a GPI vs UFH was associated with a significantly lower risk of myocardial infarction (MI; relative risk [RR] = 0.74; $P = 0.014$) and revascularization (RR = 0.64; $P = 0.008$), an increased risk of minor bleeding (RR = 1.37; $P = 0.016$), and a trend towards an increased risk of major bleeding (RR = 1.21; $P = 0.22$) and lower mortality (RR = 0.79; $P = 0.12$).¹⁹ In another meta-analysis of randomized trials comparing LMWHs vs UFH in the setting of STEMI, LMWHs were associated with a reduction in mortality of nearly 50% (RR = 0.51; $P < 0.001$) and a reduction of 32% in major bleeding (RR = 0.68; $P = 0.02$) compared with UFH. Furthermore, the benefit of LMWHs was more pronounced in patients with higher baseline risk.²⁰

In the ATOLL trial (Acute STEMI Treated with primary PCI and intravenous enoxaparin Or UFH to Lower ischaemic and bleeding events at short- and Long-term follow-up),²¹ a randomized open-label trial, LMWH (enoxaparin; 0.5 mg/kg IV followed by subcutaneous treatment) was compared with UFH. The primary composite endpoint of 30-day death, MI, procedural failure, and major bleeding was not significantly different in the enoxaparin arm (RR = 17%; $P = 0.063$), and there was no significant difference in bleeding with enoxaparin vs UFH. In the per-protocol analysis of the ATOLL trial comprising more than 87% of the study population, enoxaparin was associated with a significantly reduced primary endpoint (RR = 0.76; $P = 0.012$), mortality (RR = 0.36; $P = 0.003$), major bleeding (RR = 0.46; $P < 0.050$), and improved net clinical benefit (RR = 0.46; $P < 0.0002$). Based on these observations, in the European guidelines, it was mentioned that enoxaparin may be considered as an alternative to UFH as an anticoagulant to pPCI.²¹

Recently, there has been great controversy surrounding the role of bivalirudin versus UFH in pPCI. The first major trial to assess the utility of bivalirudin in STEMI was the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial.¹⁰ This trial was completed in 2008. Patients ($n = 3602$) who presented with STEMI within 12 hours of symptom onset were randomly treated with bivalirudin alone or heparin plus a GPI during pPCI. Bivalirudin was administered as an IV bolus of 0.75 mg/kg, followed by an infusion of 1.75 mg/kg/h. Heparin was administered as an IV bolus of 60 IU/kg of body weight, with subsequent boluses targeted to an activated clotting time of 200 to 250 seconds. A bolus dose of UFH without infusion was administered in nearly two-thirds of patients before PCI in both arms. In the bivalirudin arm, if heparin was administered before bivalirudin, then bivalirudin administration started 30 minutes later. The median activated clotting time was 357 seconds in the bivalirudin arm and 264 seconds in the heparin + GPI arm. GPI was administered for bailout

or giant thrombus occurrence in 7.5% in the bivalirudin arm. Bivalirudin therapy was associated with a reduction in the 30-day rate of net adverse clinical events (NACEs) of 24% (RR = 0.76; $P = 0.005$), mainly attributed to a lower rate of major bleeding (RR = 0.60; $P < 0.001$); significantly lower 30-day rates of cardiac (RR = 0.62; $P = 0.03$) and total death (RR = 0.66; $P = 0.047$); and an increased risk of acute (within 24 hours) but not 30-day stent thrombosis (TABLE). Finally, in patients not treated with heparin before the procedure in the bivalirudin arm, the rate of major adverse clinical events (MACEs) was 7.2% vs ~4.5%-5.2% in the other arms (P value for interaction = 0.08). The absence of a high loading dose of clopidogrel and UFH prerandomization were predictors of a higher risk of acute and subacute stent thrombosis. In HORIZONS-AMI,¹⁰ radial access was used only in 6% of the cases, clopidogrel was the major P2Y₁₂ receptor inhibitor, and 772 patients were treated with bare metal stents and 2257 patients—with paclitaxel-eluting stents.²² At 3-year follow-up, cardiac and all-cause mortality, reinfarction, and major bleeding not related to coronary artery bypass grafting (CABG) were lower in the bivalirudin arm.¹¹ The results of this trial, particularly the long-lasting mortality benefit, provided a strong rationale for recommending bivalirudin therapy in pPCI.

Important changes in clinical practice have occurred since the completion of the HORIZONS-AMI trial.¹⁰ The most notable has been the implementation of P2Y₁₂ inhibitor therapy more potent than clopidogrel and a more frequent use of radial artery access and thrombectomy. Since bivalirudin is a DTI without significant direct antiplatelet effects, it was assumed that bivalirudin plus a potent fast-acting P2Y₁₂ inhibitor such as prasugrel may be more effective than heparin plus clopidogrel therapy. In the BRAVE 4 study (Bavarian Reperfusion Alternatives Evaluation), 540 STEMI patients with planned pPCI within 24 hours from symptom onset were randomly treated with prasugrel plus bivalirudin or clopidogrel plus heparin. This study was prematurely terminated due to slow recruitment. There were no differences in 30-day primary composite endpoint of NACEs (RR = 1.09), MACEs (RR = 0.89), and major bleeding according to the HORIZONS-AMI definition (RR = 1.18) between the two groups. This trial failed to demonstrate the superiority of bivalirudin plus prasugrel therapy versus clopidogrel plus heparin therapy.²³

The next major STEMI trial to evaluate the efficacy of bivalirudin was the HEAT-pPCI trial.²⁴ Unfractionated heparin was compared with bivalirudin in pPCI in a single-center, open-label study that enrolled 1829 patients. In contrast to HORIZONS-AMI, in HEAT-pPCI, GPIs were administered selectively in both groups for massive thrombus, slow or no reflow, or a thrombotic complication (13% in the bivalirudin group and 15% in the heparin group). The median time from symptom onset to randomization was ~2.8

hours. Before angiography, a bolus dose of heparin of 70 U/kg of bodyweight was administered in the catheterization laboratory. An additional dose of heparin was administered if activated clotting time was 5 to 15 minutes after the bolus dose or at the end of the procedure was less than 200 seconds. A bolus of bivalirudin of 0.75 mg/kg followed by infusion of 1.75 mg/kg/h for the duration of the procedure was administered. A rebolus of bivalirudin of 0.3 mg/kg was administered if activated clotting time was 5 to 15 minutes after the bolus dose or at the end of the procedure was less than 225 seconds. A median activated clotting time at the end of the procedure was 251 seconds in the bivalirudin group and 224 seconds in the heparin group. The heparin dose of 70 U/kg was less than that administered in earlier studies of heparin monotherapy. Radial access was used in nearly 80% of the cases in both groups. Ticagrelor was administered in ~60% of the patients; prasugrel, in 27%; and clopidogrel, in ~10%. Bivalirudin therapy was associated with 1.5-fold higher 28-day primary efficacy outcome (RR = 1.52; $P = 0.01$) that was primarily driven by an increased rate of new MI (RR = 3.01; $P = 0.004$) and additional unplanned target lesion revascularization (RR = 4.01; $P = 0.001$), nonsignificantly higher primary safety outcome of Bleeding Academic Research Consortium major bleeding (RR = 1.15; $P = 0.59$) and nearly 3 times higher acute stent thrombosis (RR = 3.26; $P = 0.007$). The HEAPT-pPCI, a real world scenario with an unselected patient population study, demonstrated that heparin monotherapy may be superior with respect to ischemic event reduction and similar with respect to safety as compared with bivalirudin monotherapy in the presence of increased use of potent P2Y₁₂ inhibitors such as ticagrelor and prasugrel.²⁴

The next major study to assess bivalirudin efficacy in ACS was the Bivalirudin in Acute Myocardial Infarction vs Heparin and GPI Plus Heparin Trial (BRIGHT).²⁵ Patients were randomly treated with bivalirudin alone, heparin alone, or heparin plus tirofiban in a ratio of 1:1:1 ratio (n~730 per arm). All patients in the bivalirudin arm received a postprocedure infusion of bivalirudin of 1.75 mg/kg/h for a median duration of 180 minutes, and 115 patients (15.6%) thereafter received an optional dose of 0.2 mg/kg/h for a median duration of 400 minutes. Heparin was given as a bolus dose of 100 U/kg plus an additional heparin administration if the postbolus activated clotting time was less than 225 seconds. For the heparin-plus-tirofiban group, a heparin dose of 60 U/kg and tirofiban dose of 10 µg/kg boluses were given followed by a tirofiban infusion of 0.15 µg/kg/min for 18 to 36 hours. A median time from symptom onset to randomization was 6.1 hours. In this trial, conducted exclusively in China, a different formulation of bivalirudin was used. Approximately 87% of the patients had STEMI, and radial access was used in 78% of the cases. Thirty-day NACE was significantly

lower in the bivalirudin vs heparin-only groups (RR = 0.67; $P = 0.008$), which was attributed to a significantly lower major bleeding rate in the bivalirudin group (4.1% bivalirudin, 7.5% heparin, and 12.3% heparin plus tirofiban; $P < 0.001$). There were no statistically significant differences between treatments in the 30-day rates of major adverse cardiac or cerebral events ($P = 0.74$), stent thrombosis ($P = 0.77$), or acute (<24-hour) stent thrombosis (0.3% in each group).²⁵

In the European Ambulance Acute Coronary Syndrome Angiography (EUROMAX) trial,²⁶ 2218 patients within 12 hours of symptom onset with a presumed diagnosis of STEMI were randomly treated with bivalirudin alone started during transport with bailout GPI vs UFH (~90%) or LMWH. GPI therapy in the heparin arm was left to the discretion of the treating physician. The median time between study-drug initiation and coronary angiography was 50 minutes. After PCI, 93% of the patients in the bivalirudin group received a prolonged (2 hours or longer) infusion of bivalirudin, with more than two-thirds of the patients receiving the reduced dose of 0.25 mg/kg/h. The median duration of bivalirudin infusion was 268 minutes (interquartile range, 250–292). Approximately 40% of the patients received clopidogrel; ~30%, prasugrel; and approximately 27%, ticagrelor. Both femoral and radial accesses were used equally (~50% in each strategy). In EUROMAX, GPIs were used in 69% of the cases in the heparin arm and in 11.5% of the cases in bivalirudin arm. Prehospital administration of bivalirudin was associated with 40% reduction in the 30 primary endpoint of composite of all-cause death or non-CABG protocol defined major bleeding (RR = 0.60; $P = 0.001$); 28%, reduction in the secondary outcome of composite of death from any cause, reinfarction, or non-CABG major bleeding (RR = 0.72; $P = 0.02$); 57%, reduction in protocol-defined major bleeding (RR = 0.43; $P < 0.001$); 6-fold higher risk of acute stent thrombosis (RR = 6.11; $P = 0.007$); ~2-fold higher risk of reinfarction (RR = 1.93, $P = 0.08$); and no difference in death (2.9% vs 3.1%).²⁶ In a subanalysis of the EUROMAX trial comparing patients with ($n = 12$) or without acute stent thrombosis ($n = 2184$), acute stent thrombosis was mitigated by bivalirudin infusion at a PCI dose, but not by the novel P2Y₁₂ inhibitors. Similarly to the previous observation of the BRIGHT trial, prolonged infusion of higher-dose bivalirudin with a median of 4 hours after PCI may be responsible for the reduced rate of acute stent thrombosis.²⁷

Meta-analyses A recently published meta-analysis of 22 randomized trials evaluated bivalirudin, UFH, fondaparinux, UFH + GPI, and LMWH + GPI in 22 434 patients undergoing pPCI.²⁸ In this meta-analysis, the risk of 30-day MACE was higher with UFH (RR = 1.49), bivalirudin (RR = 1.34), and fondaparinux (RR = 1.78) as compared with UFH + GPI. LMWH + GPI had the greatest treatment efficacy followed by UFH +

GPI. Bivalirudin monotherapy was associated with a lower major bleeding risk compared with UFH + GPI (RR = 0.47) or UFH (RR = 0.58).²⁸ In another meta-analysis, the 5 randomized trials discussed above (HORIZONS-AMI, BRAVE-4, BRIGHT, HEAT PPCI, and EUROMAX) involving ~10000 patients with STEMI, bivalirudin therapy as compared with heparin therapy was associated with a significant reduction in protocol-defined major bleeding (odds ratio [OR] = 0.64; $P < 0.0001$) or Thrombolysis in Myocardial Infarction major bleeding (OR = 0.62; $P = 0.001$), but no difference in overall all-cause mortality (OR = 0.88; $P = 0.17$), 30-day mortality (OR = 0.90; $P = 0.40$), or overall MI (OR = 0.86; $P = 0.18$). Bivalirudin was associated with similar overall definite/probable stent thrombosis (OR = 1.18; $P = 0.22$) but higher rates of 30-day MI (OR = 1.40; $P = 0.04$) and 30-day definite/probable stent thrombosis (that included acute stent thrombosis) (OR = 1.64; $P = 0.004$).²⁹ In another meta-analysis of the same trials, results similar to the previous meta-analysis were reported.³⁰ In addition, higher rates of acute stent thrombosis (OR = 3.55; $P = 0.001$) were reported with bivalirudin therapy. There were no significant differences in 30-day rates of reinfarction (OR = 1.47; $P = 0.10$), subacute stent thrombosis (OR = 0.86; $P = 0.64$), and cardiovascular death (OR = 0.76; $P = 0.07$), and there were no interactions between bailout vs routine GPI use in the heparin arm for any safety or efficacy outcomes ($P_{\text{interaction}} > 0.10$).³⁰

Finally, a summary of the nuances between trials appears warranted.

1 HORIZONS-AMI: although considered a trial of bivalirudin vs UFH + GPI, the study was actually a comparison of UFH + in catheterization laboratory bivalirudin + bailout GPI vs UFH + standard, prolonged GPI (12–18 h), since patients were largely pretreated with heparin in both arms. Mostly femoral access, a pharmacodynamically limited P2Y₁₂ inhibitor (clopidogrel), and early generation (paclitaxel-eluting) stents were used. Bivalirudin therapy was associated with lower major bleeding and a lower mortality rate that has not been reproduced in subsequent smaller pPCI trials. A significantly increased rate of acute stent thrombosis, but not subacute stent thrombosis, was observed in the bivalirudin group—an observation that has been supported in EUROMAX despite a longer bivalirudin infusion duration and the use of more potent P2Y₁₂ inhibitors. Furthermore, a reduction in major bleeding with bivalirudin was observed. Patients with higher bleeding risk may be benefited by bivalirudin therapy, whereas patients with higher thrombotic risk may be benefited by heparin plus bailout GPI strategy.

2 The BRAVE 4 trial was prematurely terminated and failed to demonstrate the superiority of bivalirudin + prasugrel therapy vs clopidogrel + heparin therapy.

3 The HEAT-PCI trial differed from HORIZONS-AMI in many ways by being approximately one-half in size, single-center, using more potent

P2Y₁₂ inhibitors (~87%), primarily radial access (~80%), and employing selective rather than uniform GPI, administration to similar extent in both arms (~13%).

4 The BRIGHT trial was conducted in China with a different formulation of bivalirudin; clopidogrel was the major P2Y₁₂ receptor inhibitor and bivalirudin was infused for a prolonged duration in some patients, and tirofiban was infused for 18 to 36 hours in the heparin + GPI arm. Lower stent thrombosis rates and greater bleeding have been reported in East Asians undergoing PCI as compared with the Western population.³¹

5 In the EUROMAX trial, bivalirudin was infused 2 hours or longer after PCI, nearly 60% of the patients were treated with prasugrel or ticagrelor, and femoral and radial accesses were used equally. In this trial, in the heparin arm, GPI use was left to the discretion of the physician and was used in high frequency (69%). The increased risk of acute stent thrombosis was mitigated by a prolonged infusion of high-dose bivalirudin as reported in a subanalysis,²⁷ the number of events in this subgroup was too small to allow any conclusion that prolonging high-dose bivalirudin post-PCI mitigates stent thrombosis.

Conclusions The totality of the data support that the use of bivalirudin is associated with an increased hazard for early stent thrombosis as compared with strategies employing heparin + uniform GPI, heparin + bailout GPI, and heparin + optional GPI. The increased risk of early stent thrombosis with bivalirudin therapy does not appear to be mitigated by a strategy of postcatheterization laboratory administration or the use of more potent P2Y₁₂ inhibitors. Bivalirudin therapy appears to reduce serious bleeding irrespective of the access route. However, employing a strategy of bailout GPI with heparin may negate the bleeding benefit associated with bivalirudin. Finally, the mortality benefit of bivalirudin observed in HORIZONS-AMI has not been repeated in more contemporary studies or demonstrated in recent meta-analyses.

So, what is the best anticoagulant therapy during pPCI for acute myocardial infarction? Recent evidence suggests that good old, inexpensive UGH deserves strong reconsideration despite reports of pharmacologic weaknesses, particularly when used with a strategy of selective GPI therapy. The role of LMWH has been far less extensively investigated in the setting of pPCI. Data obtained in an Asian population (BRIGHT trial)²⁵ may be less relevant to a Caucasian population since bleeding is inherently higher and stent thrombosis lower despite a higher level of on-treatment platelet reactivity in the Asian population. At this time, it appears that a strategy of bivalirudin therapy in pPCI should be reserved for patients at high bleeding risk.

REFERENCES

- O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013; 61: e78-e140.
- Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012; 33: 2569-2619.
- Alonso-Organ S, Moreno-Luna R, López JA, et al. Proteomic characterization of human coronary thrombus in patients with ST-segment elevation acute myocardial infarction. *J Proteomics*. 2014; 109: 368-381.
- Helseth R, Seljeflot I, Opstad T, et al. Genes expressed in coronary thrombi are associated with ischemic time in patients with acute myocardial infarction. *Thromb Res*. 2015; 135: 329-333.
- Silvain J, Collet JP, Nagaswami C, et al. Composition of coronary thrombus in acute myocardial infarction. *J Am Coll Cardiol*. 2011; 57: 1359-1367.
- Yunoki K, Naruko T, Sugioka K, et al. Thrombus aspiration therapy and coronary thrombus components in patients with acute ST-elevation myocardial infarction. *J Atheroscler Thromb*. 2013; 20: 524-537.
- Rittersma SZ, van der Wal AC, Koch KT, et al. Plaque instability frequently occurs days or weeks before occlusive coronary thrombosis: a pathological thrombectomy study in primary percutaneous coronary intervention. *Circulation*. 2005; 111: 1160-1165.
- Quadros AS, Cambuzzi E, Sebben J, et al. Red versus white thrombi in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention: clinical and angiographic outcomes. *Am Heart J*. 2012; 164: 553-560.
- Vecchio S, Varani E, Chechi T, et al. Coronary thrombus in patients undergoing primary PCI for STEMI: Prognostic significance and management. *World J Cardiol*. 2014; 6: 381-392.
- Stone GW, Witzencbichler B, Guagliumi G, et al. HORIZONS-AMI Trial Investigators. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med*. 2008; 358: 2218-2230.
- Stone GW, Witzencbichler B, Guagliumi G, et al. HORIZONS-AMI Trial Investigators. 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; 377: 2193-2204.
- Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. *Circulation*. 2003; 108: 1664-1672.
- Mega JL, Braunwald E, Wiviott SD, et al. ATLAS ACS 2-TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med*. 2012; 366: 9-19.
- Huntington JA, Baglin TP. Targeting thrombin – rational drug design from natural mechanisms. *Trends Pharmacol Sci*. 2003; 24: 589-595.
- Bates SM, Weitz JI. The mechanism of action of thrombin inhibitors. *J Invasive Cardiol*. 2000; 12 Suppl F: 27F-32F.
- Hirsh J, Warkentin TE, Shaughnessy SG, et al. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. *Chest*. 2001; 119 (1 Suppl): 64S-94S.
- Linhardt RJ, Gunay NS. Production and chemical processing of low molecular weight heparins. *Sem Thromb Hem*. 1999; 3: 5-16.
- Kolh P, Windecker S. ESC/EACTS myocardial revascularization guidelines 2014. *Eur Heart J*. 2014; 35: 3235-3236.
- Winchester DE, Brearley WD, Wen X, et al. Efficacy and safety of unfractionated heparin plus glycoprotein IIb/IIIa inhibitors during revascularization for an acute coronary syndrome: a meta-analysis of randomized trials performed with stents and thienopyridines. *Clin Cardiol*. 2012; 35: 93-100.
- Navarese EP, De Luca G, Castriota F, et al. Low-molecular-weight heparins vs unfractionated heparin in the setting of percutaneous coronary intervention for ST-elevation myocardial infarction: a meta-analysis. *J Thromb Haemost*. 2011; 9: 1902-1915.
- Collet JP, Huber K, Cohen M, et al. A direct comparison of intravenous enoxaparin with unfractionated heparin in primary percutaneous coronary intervention (from the ATOLL Trial). *Am J Cardiol*. 2013; 112: 1367-1372.
- Stone GW, Witzencbichler B, Guagliumi G, et al. HORIZONS-AMI Trial Investigators. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med*. 2008; 358: 2218-2230.
- Schulz S, Richardt G, Laugwitz KL, et al. Bavarian Reperfusion Alternatives Evaluation (BRAVE) 4 Investigators. Prasugrel plus bivalirudin vs clopidogrel plus heparin in patients with ST-segment elevation myocardial infarction. *Eur Heart J*. 2014; 35: 2285-2294.
- Shahzad A, Kemp I, Mars C, et al. HEAT-PPCI trial investigators. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. *Lancet*. 2014; 384: 1849-1858.
- Han Y, Guo J, Zheng Y, Zang H, et al. BRIGHT Investigators. Bivalirudin vs heparin with or without tirofiban during primary percutaneous coronary intervention in acute myocardial infarction: the BRIGHT randomized clinical trial. *JAMA*. 2015; 313: 1336-1346.

- 26 Steg PG, van't Hof A, Hamm CW, et al. EUROMAX Investigators. Bivalirudin started during emergency transport for primary PCI. *N Engl J Med*. 2013; 369: 2207-2217.
- 27 Clemmensen P, Wiberg S, Van't Hof A, et al. Acute stent thrombosis after primary percutaneous coronary intervention: insights from the EUROMAX trial (European Ambulance Acute Coronary Syndrome Angiography). *JACC Cardiovasc Interv*. 2015; 8: 214-220.
- 28 Bangalore S, Toklu B, Kotwal A, et al. Anticoagulant therapy during primary percutaneous coronary intervention for acute myocardial infarction: a meta-analysis of randomized trials in the era of stents and P2Y12 inhibitors. *BMJ*. 2014; 349: g6419.
- 29 Verdoia M, Schaffer A, Barbieri L, et al. Bivalirudin as compared to unfractionated heparin in patients undergoing percutaneous coronary revascularization: A meta-analysis of 22 randomized trials. *Thromb Res*. 2015; 135: 902-915.
- 30 Capodanno D, Gargiulo G, Capranzano P, et al. Bivalirudin versus heparin with or without glycoprotein IIb/IIIa inhibitors in patients with STEMI undergoing primary PCI: An updated meta-analysis of 10,350 patients from five randomized clinical trials. *Eur Heart J Acute Cardiovasc Care*. 2015 Mar 6. [Epub ahead of print].
- 31 Levine GN, Jeong YH, Goto S, et al. Expert consensus document: World Heart Federation expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI. *Nat Rev Cardiol*. 2014; 11: 597-606.

Jaka jest najlepsza terapia przeciwkrzepliwa podczas pierwotnej przezskórnej interwencji wieńcowej w świeżym zawale serca?

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SŁOWA KLUCZOWE

antykoagulanty,
incydenty
niedokrwienne,
krwawienie,
pierwotna przezskórna
interwencja
wieńcowa, zawał
serca z uniesieniem
odcinka ST

STRESZCZENIE

Zarówno zawał serca z uniesieniem odcinka ST, jak i przezskórna interwencja wieńcowa (PCI) są stanami wysoce prozakrzepowymi, a trombina odgrywa kluczową rolę w procesie powstawania skrzepliny prowadzącym w konsekwencji do wystąpienia incydentów niedokrwienych. Dlatego też strategię leczenia przeciwkrzepliowego w skojarzeniu z podwójną terapią przeciwplatekową uznano *de facto* za standard leczenia podczas pierwotnej PCI. Ostatnio duże kontrowersje wzbudza rola biwalirudyny w porównaniu z heparyną niefrakcjonowaną podczas pierwotnej PCI. Upřednio wyniki badania HORIZONS-AMI, zwłaszcza długoterminowa korzyść w postaci zmniejszenia śmiertelności, stanowiły silne uzasadnienie dla zalecania terapii biwalirudyną w pierwotnej PCI. Jednak korzystnego wpływu biwalirudyny na śmiertelność zaobserwowanego w badaniu HORIZONS-AMI nie potwierdzono w nowszych badaniach ani nie wykazano w niedawno przeprowadzonych metaanalizach. Niniejsze opracowanie stanowi zwięzły przegląd danych na temat kontrowersji wokół optymalnej terapii przeciwkrzepliowej w pierwotnej PCI. Wyniki ostatnich badań sugerują, że zdecydowanie należy ponownie zastanowić się nad stosowaniem heparyny niefrakcjonowanej (mimo doniesień o słabych stronach tego leku), w szczególności nad jej skojarzeniem ze strategią selektywnej blokady receptora GP IIb/IIIa. Wydaje się, że strategię terapii biwalirudyną w pierwotnej PCI należy zarezerwować dla chorych obciążonych dużym ryzykiem krwawienia.

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