Editorial

Bivalirudin and the Matrix Trial: The End of the Story?

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In the last decades, there has been considerable interest in the improvement of antithrombotic therapy for patients with acute coronary syndromes (ACS) undergoing coronary angioplasty [1-4].

Bivalirudin due to its pharmacological properties, is supposed to offer several advantages compared with traditional unfractionated heparin (UFH) [5]. Firstly, bivalirudin is a direct thrombin inhibitor and can, therefore, selectively block clot-bound thrombin, potentially achieving a more potent and more predictable anticoagulant response than UFH. Moreover, bivalirudin can also display an antiplatelet effect, which could contribute to further benefits for patients undergoing percutaneous coronary interventions (PCI) and has therefore being proposed as an alternative strategy to UFH with adjunctive glycoprotein IIb-IIIa inhibitors (GPIs) [5]. The change in the therapeutic strategy has mainly been driven by the observed lower rate of bleeding complications with bivalirudin. In fact, major bleeding in the setting of PCI has been associated with increased major adverse cardiac events, longer in-hospital stay and higher mortality [6], despite the use of the radial approach which has significantly reduced these complications [7].

While bivalirudin may sound new to young cardiologists, this drug has been considered for more than 20 years as a potential alternative strategy for anticoagulation in patients undergoing PCI. In fact, initial randomized trials were conducted between 1990 and 1998, all reaching negative results compared with UFH, which therefore has been regarded as the anticoagulant of choice in subsequent years. An appraisal of bivalirudin came out later, with additional large studies conducted in elective PCI (REPLACE 2 trial) [8] and ACS (ACUITY trial) [9]. Both studies showed a consistent reduction in bleeding complications, which however did not translate into benefits in ischemic complications and mortality. Similar findings have been observed in the ISAR-REACT 3 and 4 [10]. In 2008, the results of the HORIZONS trial surprisingly provided strong data in support of bivalirudin showing in the setting of ST-elevation myocardial infarction (STEMI), beyond the reduction in major bleeding, a significant reduction in mortality and re-infarction, despite the higher risk of acute (< 24 h) risk of stent thrombosis [4]. However, several other studies have subsequently been conducted, and they did not confirm these benefits. In particular, the large HEAT PPCI [11], comparing bivalirudin *vs*. UFH in STEMI patients undergoing primary PCI (pPCI), showed no beneficial effects in mortality and bleeding complications. This study confirmed the significantly higher risk of stent thrombosis with bivalirudin, which has been consistently observed in almost all major randomized trials. The absence of benefits in ischemic complications and mortality in the setting of STEMI, despite the benefits in major bleeding, has also been observed in the BRIGHT trial [12].

The recent EUROMAX trial [13] investigated the potential benefits of bivalirudin as upstream administration. This study randomly assigned 2218 STEMI patients who were being transported for pPCI to receive either bivalirudin or UFH or low molecular weight heparin with optional GPIs (control group). There was no beneficial effect in pre-procedural recanalization nor in ST-segment resolution. In addition, no benefits were observed in mortality and re-infarction with a 5-fold increase in the risk of acute stent thrombosis (1.1 *vs.* 0.2%; relative risk, 6.11; 95% CI, 1.37 to 27.24; P=0.007). No difference was observed in Thrombolysis in Myocardial Infarction (TIMI) flow and major bleeding complications.

A Meta-analysis has been conducted showing that in the setting of STEMI [14] bivalirudin, compared with a strategy of UFH with/or without GPIs, does not provide benefits in terms of mortality and re-infarction, with higher risk of stent thrombosis, despite the significant reduction in major bleeding complications.

The higher risk of in stent thrombosis has been attributed to the short half-life (2.5 h) of bivalirudin, which therefore, while contributing the reduction in bleeding complications, does not protect from the occurrence of thrombotic complications [14]. In fact, in the context of pPCI, even new oral adenosine diphosphate (ADP) antagonists have shown a delayed onset of action that would create a window of suboptimal inhibition of platelet aggregation. Therefore, it was suggested that a prolonged post-procedural infusion of bivalirudin would have masked this Achilles' heel of bivalirudin. This suggestion have been followed by

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many clinicians and even recommended in the recent non-STEMI (NSTEMI) guidelines [15], simply based on intuition that is still missing any scientific evidence.

The MATRIX trial [16] has recently been published and presumably represents the last randomized trial that will be conducted on bivalirudin. This is a large multicenter trial, including > 7000 ACS patients that aimed at shedding light on several relevant issues, concerning the choice of access and optimal antithrombotic therapy. Patients were randomly assigned to femoral *vs*. radial approach, and to bivalirudin *vs.* UFH. An additional randomization was performed among patients receiving bivalirudin to test the advantages of prolonged post-procedural infusion.

It is obvious that the complexity of the study design increases the risk of type 1 error and therefore strongly limits any conclusions. However, it remains a relevant study due to the large number of patients. The positive features of this trial are the mean age of 65 years, higher than that observed in other similar randomized trials, as much as the inclusion of about 8% of patients with advanced Killip class at presentation. About 55% of the patients had STEMI. The study did not show any significant benefit in terms of primary endpoints. No interaction was observed with major baseline features, with the only exception of body weight. In fact, bivalirudin performed better in patients with high body weight, whereas opposite findings were observed among patients with low body weight. In addition, post-procedural infusion was associated with even higher risk of subacute stent thrombosis, without any benefit in overall occurrence of stent thrombosis.

Some factors limit the value of study. Many patients in the bivalirudin group also received UFH, either upstream (in 32.3% of the patients) or during or after the catheterization laboratory (in 6.9% of the patients). It is very difficult to enroll patients in studies that prohibit the initial use of UFH. However, as demonstrated in the HORIZONS trial and the large prospective non randomized Swedish experience [17], such a use improves the outcome of patients receiving bivalirudin and is therefore confounding.

The authors [16] observed a significant reduction in cardiovascular mortality (1.6 *vs*. 2.3% Risk Ratio [95% CI] = 0.70 (0.49-0.98), p = 0.04). However, the investigators analyzed several end points with multiple randomizations, so it is to be expected that at least one end point would be positive by chance, having performed no correction for multiple comparisons.

The MATRIX trial [16] represents the last piece of the puzzle and contributed to put an end to the story of bivalirudin as routine anticoagulation of ACS and STEMI patients. Bivalirudin should certainly be downgraded in guidelines, given that prolonged infusion failed to overcome the higher risk of stent thrombosis observed in almost all randomized trials conducted so far using bivalirudin. This is especially important with the extensive use of the radial approach and protamine administration to reverse UFH action that have contributed to minimize the risk of bleeding complications [18]. While bleeding should certainly be regarded as a relevant endpoint, it should not significantly influence the choice of optimal antithrombotic therapy aiming at the reduction of re-infarction and thrombotic complications [19]. In fact, almost all randomized trials and meta-analyses so far conducted have failed to show an association between reduction in bleeding complications and reduction in mortality obtained with new antithrombotic therapies [14].

Special attention should be paid to high-risk patients such as those with STEMI undergoing pPCI, where our priority still remains a rapid and optimal inhibition of platelet aggregation with the aim of early recanalization, especially in the first hours (the *golden hours*). New oral ADP-antagonists have failed to achieve with the loading dose an optimal rapid inhibition of platelet aggregation in the setting of STEMI as compared with that observed in healthy subjects [20, 21], due to a delayed drug absorption [22] and increased baseline platelet reactivity [23]. In addition, a change of thrombus composition across the time from plaque rupture and coronary occlusion has been described, with more platelets in the early phase [24]. Therefore, GPIs [25] and the coming cangrelor [26] could be the key elements of an optimal reperfusion strategy and considered as upstream therapy for our high-risk STEMI patients presenting in the early (< 4 h) phase of infarction.

CONFLICT OF INTEREST

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REFERENCES

[1] De Luca G, Marino P. Advances in antithrombotic therapy as adjunct to reperfusion therapies for ST-segment elevation myocardial infarction. Thromb Haemost 2008; 100: 184-95.

[2] De Luca G, Suryapranata H, Stone GW, *et al*. Abciximab as adjunctive therapy to reperfusion in acute ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. JAMA 2005; 293: 1759-65.

[3] De Luca G, Smit JJ, Ernst N, *et al*. Impact of adjunctive tirofiban administration on myocardial perfusion and mortality in patients undergoing primary angioplasty for ST-segment elevation myocardial infarction. Thromb Haemost 2005; 93: 820-3.

[4] Stone GW, Witzenbichler B, Guagliumi G, *et al*.; HORIZONS-AMI Trial Investigators. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008; 358: 2218-30.

[5] Warkentin TE, Greinacher A, Koster A. Bivalirudin. Thromb Haemost 2008; 99: 830-9.

[6] Manoukian SV, Feit F, Mehran R, *et al*. Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes: an analysis from the ACUITY Trial. J Am Coll Cardiol 2007; 49: 1362-8.
[7] De Luca G, Schaffer A, Wirianta J, Suryapranata H. Comprehensive meta-analysis of radial *vs*. femoral approach in primary angioplasty for STEMI. Int J Cardiol 2013; 168: 2070-81.
[8] Lincoff AM, Bittl JA, Harrington RA, *et al*.; REPLACE- 2 Investigators. 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; 289: 853-63.
[9] Stone GW, White HD, Ohman EM, *et al*.; Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial investigators. 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.
[10] Shulz S, Kastrati A, Ferenc M, *et al*. One-year outcomes with abciximab and unfractionated heparin versus bivalirudin during percutaneous coronary interventions in patients with non-ST-segment elevation myocardial infarction: updated results from the ISAR-REACT 4 trial. EuroIntervention 2013; 9: 430-6.
[11] 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: 1849-58.
[12] Han Y, Guo J, Zheng Y, *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: 1336-46.
[13] Steg PG, van't Hof A, Hamm CW, *et al*.; the EUROMAX Investigators. Bivalirudin Started during Emergency Transport for Primary PCI. N Engl J Med 2013; 369: 2207-17.
[14] Verdoia M, Schaffer A, Barbieri L, Suryapranata H, De Luca G. Bivalirudin as compared to unfractionated heparin in patients undergoing percutaneous coronary revascularization: A meta-analysis of 22 randomized trials. Thromb Res 2015; 135: 902-15.
[15] Authors/Task Force Members, Roffi M, Patrono C, Collet JP, *et al*. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2015 Aug 29. pii: ehv320. [Epub ahead of print].
[16] Valgimigli M, Frigoli E, Leonardi S, *et al*.; MATRIX Investigators. Bivalirudin or Unfractionated Heparin in Acute Coronary Syndromes. N Engl J Med 2015; 373: 997-1009.
[17] Koutouzis M, Lagerqvist B, James S, *et al*. Unfractionated heparin administration in patients treated with bivalirudin during primary percutaneous coronary intervention is associated lower mortality and target lesion thrombosis: a report from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). Heart 2011; 97: 1484-8.
[18] De Luca G, Parodi G, Antoniucci D. Safety and benefits of protamine administration to revert anticoagulation soon after coronary angioplasty. A meta-analysis. J Thromb Thrombolysis 2010; 30: 452-8.
[19] De Luca G, Dirksen MT, Spaulding C, *et al*.; DESERT cooperation. Time course, predictors and clinical implications of stent thrombosis following primary angioplasty. Insights from the DESERT cooperation. Thromb Haemost 2013; 110: 826-33.
[20] Parodi G, Valenti R, Bellandi B, *et al*. Comparison of prasugrel and ticagrelor loading doses in ST-segment elevation myocardial infarction patients: RAPID (Rapid Activity of Platelet Inhibitor Drugs) primary PCI study. J Am Coll Cardiol 2013; 61: 1601-6.
[21] Montalescot G, van't Hof AW, Lapostolle F, *et al*.; ATLANTIC Investigators. Prehospital ticagrelor in ST-segment elevation myocardial infarction. N Engl J Med 2014; 371: 1016-27.
[22] Heestermans AA, van Werkum JW, Taubert D, *et al*. Impaired bioavailability of clopidogrel in patients with a ST-segment elevation myocardial infarction. Thromb Res 2008; 122: 776-81.
[23] Mikhailidis DP, Barradas MA, Mier A, *et al*. Platelet function in patients admitted with a diagnosis of myocardial infarction. Angiology 1987; 38: 36-45.
[24] Silvain J, Collet JP, Nagaswami C, *et al*. Composition of coronary thrombus in acute myocardial infarction. J Am Coll Cardiol 2011; 57: 1359-67.
[25] De Luca G, Savonitto S, Van't Hof AW, Suryapranata H. Platelet GP IIb-IIIa Receptor Antagonists in Primary Angioplasty: Back to the Future. Drugs 2015; 75: 1229-53.
[26] Keating GM. Cangrelor: A Review in Percutaneous Coronary Intervention. Drugs 2015; 75: 1425-3.

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