Current Perspectives on Anticoagulation in Patients With STEMI

Written by Nicola Parry

In a symposium on the management of individuals with STEMI, 3 speakers highlighted key aspects of anticoagulation in the management of these patients.

Patrick Goldstein, MD, Lille University Hospital, Lille, France, discussed the importance of initiating antithrombotic therapy in patients with STEMI undergoing primary percutaneous intervention (PPCI).

Prof Goldstein shared data from the ATOLL trial [Montalescot G et al. *Lancet*. 2011] in which patients undergoing PPCI experienced clinical benefit with enoxaparin as compared with standard unfractionated heparin (UFH) therapy. The primary end point of the study was not reached, with data showing no significant difference in the 30-day incidence of death, complication of myocardial infarction (MI), procedural failure, or major bleeding between the groups ($P = .07$). However, enoxaparin had a good safety profile, and patients treated with this low-molecular-weight heparin (LMWH) experienced clinical benefit compared with UFH with respect to the secondary end point of death, recurrent MI, acute coronary syndrome, or urgent revascularization ($P = .016$).

The EUROMAX trial [Steg PG et al. *N Engl J Med*. 2013] compared bivalirudin with standard UFH or LMWH therapy, with or without a glycoprotein inhibitor (GPI), in patients being transported by ambulance for PPCI. The study reached its primary end point of death or non-coronary artery bypass graft (CABG)–related major bleeding at 30 days ($P = .002$) and its secondary end point of death, reinfarction, or major bleeding at 30 days ($P = .03$), demonstrating significant clinical benefit of bivalirudin over standard therapy. Non-CABG–related major bleeding at 30 days was also significantly reduced ($P < .001$) with bivalirudin.

Uwe Zeymer, Klinikum Ludwigshafen, Ludwigshafen, Germany, discussed that although UFH has been the standard of care for patients with STEMI undergoing PPCI for some time, its optimum dose remains uncertain because of a lack of prospective and randomized clinical trial data.

The HEAP trial [Liem A et al. *J Am Coll Cardiol.* 2000] demonstrated that heparin exerts no effect on clot lysis in patients prior to PPCI, even at high doses, which are associated with increased bleeding risk. Prof Zeymer emphasized that LMWHs may therefore represent a better alternative to UFH in this patient population. After injection, these agents produce a level of anticoagulation for approximately 2 hours that is sufficient to perform PPCI. He added that the ATOLL trial [Montalescot G et al. *Lancet*. 2011] produced the first pure comparison of 2 anticoagulation regimens and showed that a single injection of enoxaparin produced an effective and safe level of anticoagulation in individuals with PPCI, results that were confirmed in a subsequent meta-analysis [Silvain J et al. *BMJ*. 2012].

Considering the direct thrombin inhibitor bivalirudin, Prof Zeymer discussed some of its advantages, including the lack of requirement of antithrombin-3 and frequent monitoring. Data from the HORIZONS-AMI trial showed decreased mortality and bleeding complications in patients with STEMI undergoing PPCI who received bivalirudin compared with heparin plus a GPI [Stone GW et al. *N Engl J Med.* 2008]. Subsequent data highlighted that 3-year mortality was reduced, even in patients treated with bivalirudin who experienced no bleeding, although the effect was more pronounced in those with bleeding [Stone GW et al. *J Am Coll Cardiol.* 2014].

Prof Zeymer also discussed the HEAT-PPCI trial [Shahzad A et al. *Lancet.* 2014] that compared anticoagulation with UFH vs bivalirudin. The bailout use of GPI therapy was relatively low (15% vs 13%), and the incidence of the primary end point (major adverse cardiac events [MACE]), and bleeding, were decreased in patients treated with UFH. A similar patient population was

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subsequently evaluated in the EUROMAX trial [Zeymer U et al. *Eur Heart J.* 2014]. Treatment with bivalirudin did not reduce death or MI but did reduce major bleeding.

BRIGHT [NCT01696110] is a recently completed study in China that compared bivalirudin monotherapy with heparin monotherapy and heparin plus tirofiban, in patients with acute MI who were eligible for PPCI. Bivalirudin monotherapy reduced the rate of net adverse cardiovascular events compared with the other regimens ($P < .001$).

Kurt Huber, MD, Wilhelminenhospital, Vienna, Austria, discussed recent updates to the European Society of Cardiology (ESC) guidelines on myocardial revascularization for antithrombotic treatment in patients with STEMI undergoing PPCI [Windecker S et al. *Eur Heart J.* 2014].

In the 2014 ESC guidelines, anticoagulation is recommended for all patients in addition to antiplatelet therapy during PPCI. From 2010 to 2012, Prof Huber noted that the only changes in the guidelines were the introduction of enoxaparin (with a Class IIa, Level B recommendation based on the data from studies such as ATOLL) [Montalescot G et al. *Lancet* 2011] and the upstream use of GPI therapy (Class IIb, Level B recommendation) [Steg PG et al. *Eur Heart J*. 2012; Wijns W et al. *Eur Heart J.* 2010].

Also in the 2014 ESC guidelines for the treatment of patients with STEMI, because of emergence of data from various clinical trials including EUROMAX, bivalirudin now carries a Class IIa, Level A recommendation, compared with its previous Class I, Level B recommendation. Conversely, because of a lack of data, the use of UFH carries a Class I, Level C recommendation.

Prof Huber also discussed the guidelines of the updated 2013 American College of Cardiology Foundation and American Heart Association for the management of STEMI, in which the use of UFH also carries a Class I, Level C recommendation [O'Gara PT et al. *J Am Coll Cardiol.* 2013]. However, bivalirudin with or without prior treatment with UFH still carries a Class I, Level B recommendation as adjunctive treatment in PPCI because these guidelines were produced prior to publication of the EUROMAX and HEAT PPCI trial results.

In conclusion, Prof Huber noted that, as in the ESC guidelines, the use of fondaparinux as the sole anticoagulant for PPCI carries a Class III, Level B recommendation, and enoxaparin has no treatment role in PPCI-treated patients with STEMI in the United States. In contrast, for patients with STEMI managed with a fibrinolytic strategy, fondaparinux carries a Class I, Level B recommendation (based on results from OASIS-6), and enoxaparin carries a Class I, Level A recommendation.

Prof Goldstein indicated that studies have shown a direct correlation between initiating anticoagulation therapy in the ambulance setting and patient survival. He noted the impact of total ischemic time on survival in these individuals, emphasizing that prehospital therapy provides more clinical benefits when patients are treated earlier. Prof Zeymer also emphasized that he no longer advocates the use of UFH for anticoagulation therapy. He recommends bivalirudin as the agent of choice in patients with high bleeding risk, whereas a combination of enoxaparin and GPI therapy is useful for individuals with high ischemic and low bleeding risk. In very low-risk patients, a combination of enoxaparin with aspirin and prasugrel or ticagrelor may provide adequate anticoagulation, he concluded.