Bleeding and thrombosis risk with bivalirudin and unfractionated heparin: re-visiting HORIZONZ, EUROMAX and HEAT-PPCI studies

Riesgo de sangrado y trombosis con bivalirudina y heparina o fracionada: análisis de los estudios HORIZONZ, EUROMAX y HEAT-PPCI

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In recent years direct thrombin inhibitors such as bivalirudin became a standard of care after results of a major controlled randomized trial was available: HORIZONS AMI (Harmonizing Outcomes with revascularizatiON and Stents in Acute Myocardial Infarction) reported[1] a net clinical benefit with use of bivalirudin compared to unfractioned heparin (UFH) plus routine IIb/IIIa glycoproteins (GPI). More recently two other randomized trials reported additional data[2,3] about which would be the ideal antithrombotic strategy during percutaneous coronary interventions (PCI) in acute myocardial infarction (MI), EUROMAX (European Ambulance Acute Coronary Syndrome Angiography) and more recently HEAT-PPCI (How Effective Are Antithrombotic Therapies in Primary PCI). Study designs from these three trials were different; although major differences were HORIZONS compared UFH plus routine IIb/IIIa GPI in the others two GPI was provisional or bail out in both experimental and control arm.

Follow-up was 3 years in HORIZONS-AMI and is planned for 1 year in EUROMAX and HEAT-PPCI (currently complete at 30 days). The three trials were powered for 30-day primary endpoints.

Time when the research was conducted deferred among trials, HORIZONS was conducted some years ago when more active thienopiridines (P2Y12) such as ticagrelor and prasugrel were not available. In EUROMAX prasugrel and ticagrelor were used in over 61% of cases and in almost 90% of HEAT-PPCI patients. Both prasugrel and clopidogrel are linked with low rate of stent thrombosis compared to clopidogrel, although they are also associated with high bleeding risk[4,5].

In HORIZONS femoral access was the rule in 95% whereas in EUROMAX and HEAT PPCI radial access were used in nearly 64% and 80% of cases respectively, and radial access in patients with PCI in STEMI have been demonstrated a significant reduction of bleeding complications in the vascular access site. The radial artery approach leads to a more than 70% reduction in bleeding at the vascular access site[6].

Immediately after HEAT PPCI reported its negative results, greater stent thrombosis without any bleeding benefit with the use of bivalirudin, a large amount of disagreement with routinely use of this drug began and a firestorm of controversy regarding the optimal anticoagulant therapy during PCI in AMI was initiated: cost effectiveness of bivalirudin was now under fire[7].

However, some limitations with HEAT PPCI have been described and criticized:

First concern was they under dosing of bivalirudin in HEAT-PCI; median activated clotting time at procedure end was only 241 s compared with 322 s in HORIZONS-AMI.

Secondly, bailout GPI use was high among bivalirudin-treated patients (13%), which may have contributed to bleeding in bivalirudin-treated patients.

Third, HEAT-PPCI also used a nonstandard definition of reinfarction, allowing stent thrombosis to serve as a surrogate included patients without enzymes rise.

Finally, HEAT-PPCI represents a single center experience; therefore results with this kind of trials should not be conclusive,they must be taken with caution and will need further assessment.

Conversely a recent pooled data[8] from two major multicenter studies: HORIZONS-AMI and EUROMAX reported a large safety/efficacy advantage with

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the use of bivalirudin. In this pooled information, authors used a patient-level data for each study, which is the most reliable and strength method to conduct this kind of research and meta-analysis.

They collected 5800 patients from over 180 sites from USA, Europe, Israel and South-America including Argentina.

Of interest EUROMAX statistical analysis plan pre-specified the pooled data reported for the authors. 30-day HORIZONS-AMI and EUROMAX databases were combined for an overallpooled analysis and assessment of heterogeneity between the 2 studies and across important subgroups. A composite end point of net adverse clinical events (NACE) major adverse cardiac events (MACE) or protocol-defined non-CABG major bleeding was used.

The main results from this pooled analysis of the HORIZONS-AMI and EUROMAX trials are that among patients undergoing primary PCI randomized to bivalirudin with provisional GPI use versus heparin with routine or bailout GPI use, at 30 days bivalirudin was associated with:

1. Significantly reduced major and minor bleeding, measured by the protocol definition and the TIMI scale, thrombocytopenia, and blood transfusions;
2. Increased rates of acute stent thrombosis, with non-significantly different rates of sub-acute stent thrombosis;
3. Non significantly different rates of all-cause mortality, although cardiac mortality was reduced.
4. Non significantly differentrates of reinfarction, ischemic driven revascularization, stroke, and MACE;
5. Substantial overall net patient benefit, evidenced by greater freedom from 30-day NACE.

Of interest these benefits were consistent across subgroups including age, presence of diabetics, vascular access site, P2Y12 inhibitor loading and maintenance dose and geographic location.

This pooled findings are in agreement with the recent presented although un-published BRIGHT (Bivalirudin in Acute Myocardial Infarction vs Glycoprotein IIb/IIIa and HeparinUndergoing Angioplasty) trial[9] in which 2,194 were randomized to bivalirudin versus heparin alone versus heparin plus GPI, bleeding rates were lowest with bivalirudin, intermediate with heparin only, and highest with heparin plus GPI, with comparable 30-day and 1-year adverse cardiac events rates in the 3 groups. Moreover, in BRIGHT, the rate of acute stent thrombosis was not increased with bivalirudin, possibly because of the routine use of a 4-h post-PCI bivalirudin infusion.

Take home message

Direct thrombin inhibitor used during PCI in AMI appears to be associated with better net safety profile when compared to UFH plus routinely or provisional GPI. Amount of benefit was consistent across subgroupsand was independently for multiple variables.

However, results of HEAT PPCI should also be taking in account and may suggest that when GPI are not used routinely and in presence of current more active P2Y12 if radial artery access was performed , UFH could be a reasonable cost/effective option.

In contrast, when the use of femoral access site was the rule such is the case of most patients treated in USA and Argentina in now days (86% and 92.8% respectively) and/or if routine GPI is planned during primary PCI[10,11], bivalirudin appears to be the first option.

Finally, differences in cost between both strategies should also be consideredin clinical decision making when coverage from the social security system is uncertain.

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