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Lessons from the trials

HEAT-PPCI: A clear and welcome win for heparin

Ahmed M. ElGuindy*

Division of Cardiology, Aswan Heart Centre, Egypt
*Email: ahmed.elguindy@myf-egypt.org

ABSTRACT
The use of bivalirudin during primary percutaneous coronary intervention (PPCI) is perceived to be associated with less bleeding compared to unfractionated heparin (UFH). However, evidence supporting this observation is confounded by the frequent co-administration of glycoprotein IIb/IIIa inhibitors in the UFH arm in the majority of previous large trials. The "How Effective Are Antithrombotic Therapies in Primary PCI (HEAT-PPCI)" trial was conducted to test the efficacy and safety of UFH vesrus bivalirudin in patients undergoing PPCI when GP IIb/IIIa inhibitors are used selectively.

Keywords: HEAT-PPCI, STEMI, primary PCI, unfractionated heparin, bivalirudin

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INTRODUCTION

Adjunctive antiplatelet and anticoagulant therapy with primary percutaneous coronary intervention (PPCI) is essential to reduce thrombotic complications and mortality. Current practice guidelines recommend pre-procedural administration of aspirin *plus* a loading dose of one of the three approved $P2Y_{12}$ inhibitors – clopidogrel, prasugrel, or ticagrelor (all *Class I, LOE B*). The currently-approved, intra-procedural anticoagulant regimens are the direct thrombin inhibitor bivalirudin, unfractionated heparin (UFH) and IV enoxaparin (the latter recommended in European, but not American guidelines).[1,2] Owing to the survival benefit and reduced rates of bleeding observed with bivalirudin in the HORIZONS-AMI trial,[3,4] the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines recommend the use of bivalirudin monotherapy, in preference to *the combination* of UFH and GP IIb/IIIa inhibitors in patients at high risk of bleeding (*class IIa, LOE B*).[2] A stronger and broader recommendation – that does not limit the preference of bivalirudin to patients at high risk of bleeding – is made by the European Society of Cardiology (ESC) (*class I, LOE B*).[1] Importantly, HORIZONS-AMI compared bivalirudin monotherapy to UFH *plus* routine GPIIb/IIIa inhibitors. The superiority of bivalirudin – compared to heparin (both UFH and enoxaparin) in terms of bleeding – was also shown in the more recent EUROMAX study.[5] Both HORIZONS-AMI and EUROMAX showed an increased rate of stent thrombosis in the bivalirudin group, however, this did not translate into worse clinical outcomes. Whether bivalirudin is superior to UFH when GPIIb/IIIa inhibitors are used selectively (with either) is not well defined. The "How Effective Are Antithrombotic Therapies in Primary PCI (HEAT-PPCI)" trial was designed to answer this question.

THE STUDY

In a session that stirred a lot of debate, results of the HEAT-PPCI trial were recently presented at the 63rd Annual American College of Cardiology/i2 Scientific Meeting in Washington DC. HEAT-PPCI was a prospective, single-center, all-comers trial that randomized 1829 consecutive patients with ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI), to either unfractionated heparin (UFH) or to bivalirudin. Patients in the heparin arm received 70 units of UFH/kg, while those in the bivalirudin arm received a bolus of 0.75 mg/kg, followed by an infusion of 1.75 mg/kg/hour for the duration of the procedure. All patients received pre-procedural dual antiplatelet therapy, and selective (bailout) use of GPIIb/IIIa inhibitors was allowed in both arms. The study was conducted at the Liverpool Heart and Chest Hospital in the United Kingdom and was supported by unrestricted grants from The Medicines Company, Parsippany, N.J., and AstraZeneca, Wilmington, Del.

The primary efficacy outcome measure was major adverse cardiovascular events (MACE) – defined as all-cause mortality, cerebrovascular accident, reinfarction, or additional unplanned target lesion revascularization (TLR). The primary safety outcome measure was major bleeding – defined as type 3 to 5 bleeding as per the Bleeding Academic Research Consortium (BARC) definitions. The mean age of the study population was 63 years, and 29% were women. Radial artery access was used in more than 80% of patients (80.3% and 82% in the bivalirudin and heparin arms respectively). Thrombus aspiration was performed in 59% and a drug-eluting stent (DES) was used in 80% of patients. In addition to aspirin, patients were loaded with guideline-recommended doses of clopidogrel (12%), prasugrel (27%), or ticagrelor (61%).

RESULTS

At 28 days, the primary efficacy end-point occurred in 8.7% of patients in the bivalirudin arm and 5.7% of patients in the UFH arm, an absolute increased risk of 3% (RR = 1.52, 95% CI = 1.1–2.1, $p = 0.01$). The difference was primarily driven by reinfarction and TLR rates, with a strongly significant (4-fold) increase in stent thrombosis observed in the bivalirudin group compared to the UFH group (3.4% vs. 0.9% respectively; RR = 3.91, 95% CI = 1.6–9.5, $p = 0.001$). Major and minor bleeding did not differ between both groups. Bailout GP IIb/IIIa inhibitors were used in 13.5% of patients in the bivalirudin group and 15.5% in the UFH group. Further data on specific subgroups will be available when the trial's results are published.

DISCUSSION

To put these results in clinical perspective, several points warrant consideration. The investigators are to be commended for conducting a very well-designed trial that addresses an extremely important question. Successfully completing patient enrollment in 22 months, and the use of contemporary therapies, ensured that the results are applicable to current practice. The "delayed consenting" design (see later), adherence to an "every patient, every time" recruitment strategy, and limiting the exclusion criteria to active bleeding at presentation and/or presence of contraindications to one of the trial medications, led to a study cohort that closely resembles "real-life" patients. Most impressively, the achieved mean door-to-device time was a mere 29 minutes. Another interesting feature of the study's design is separating efficacy and safety outcome measures, namely ischemic events and bleeding, which tend to move in opposite directions. While both probably carry a similar impact on mortality, combining them into a composite endpoint creates methodological and analytical problems that might impair full understanding of the true benefits and risks associated with each drug.

Ischemic end-points

Essentially driven by increased rates of reinfarction and acute stent thrombosis, the study's primary efficacy outcome showed a statistically significant difference in favor of UFH. The 4-fold increase in stent thrombosis mirrors the rates previously observed in HORIZONS-AMI and EUROMAX. Bivalirudin was administered at the manufacturer-recommended dose of a 0.75 mg/kg followed by an infusion of 1.75 mg/kg/hour. The activated clotting time (ACT), monitored using a validated point-of-care machine known to give values 50 seconds less than other commercially available machines, was higher in the bivalirudin group compared to the UFH group (270 s vs. 236 s respectively). ACTs were measured 5–15 minutes after administration of the drugs and extra boluses were given when appropriate. Collectively, these facts strongly refute the argument that bivalirudin might have been underdosed in HEAT-PPCI. There is a possibility that a prolonged (4 hours after PCI) high-dose infusion of bivalirudin might have narrowed the gap with UFH, but this remains highly speculative. It is worth mentioning that bivalirudin, at the normal dose, costs approximately 400 times as much as heparin. This difference can rise to a staggering 1500-fold if a prolonged infusion strategy is used.

Bleeding

An equally important finding in HEAT-PPCI was the lack of differences in bleeding complications between both groups (major bleeding in 3.5% of the bivalirudin group vs. 3.1% in the UFH group; RR = 1.15, 95% CI = 07–1.9, $p = 0.59$). This held true regardless of the arterial access used during the procedure. At first glance, this seems to contradict data from previous large randomized trials, all of which confirmed less bleeding rates with bivalirudin. A closer look at these trials however highlights a frequently overlooked fact; *none* of them performed a real head-to-head comparison between UFH and bivalirudin (in the PPCI setting), with discretionary bailout use of GPIIb/IIIa. HORIZONS-AMI and REPLACE-2 compared bivalirudin alone to heparin plus routine GPIIb/IIIa inhibitors.[3,6] The use of "bailout" GPIIb/IIIa in the bivalirudin group was allowed in both studies (≈7% in both). EUROMAX, the only other large randomized trial designed to test bivalirudin vs. heparin (UFH or enoxaparin) with selective bailout use of GPIIb/IIIa inhibitors, ended up with markedly nonhomogeneous study groups in terms of GPIIb/IIIa inhibitors administration rates (11.5% in the bivalirudin group vs. 69.1% in the heparin arm), which obviously makes a reliable direct comparison between the two tested anticoagulants very difficult.

Taken together, these observations strongly suggest that the lower bleeding risks previously observed with bivalirudin seem to be essentially driven by the confounding effect of administering GPIIb/IIIa inhibitors routinely with heparin. In fact, the ACUITY trial (conducted in non-STEMI patients) showed equal bleeding rates in the two arms where routine GPIIb/IIIa inhibitors were used; with the third arm being bivalirudin monotherapy which unsurprisingly showed lower bleeding rates.[7] It is for these reasons (plus the routine use of high loading doses of oral antiplatelets), that highly-selective use of GPIIb/IIIa inhibitors in PPCI has increasingly become the recommended strategy.
Selective/bailout use of GPIIb/IIIa inhibitors is the currently recommended strategy by both the ESC and ACCF/AHA. Older trials simply do not provide sufficient data on the safety of UFH compared to bivalirudin when this strategy is adopted.

Ethical concerns

Another contentious aspect to HEAT-PPCI was its unique "delayed-consent" design, whereby patients were randomized and treated without prior consenting to participate in the study. Written consent was thereafter obtained during the recovery period and reconfirmed at 28 days. At the end of the 28-day period, only 3 patients refused consenting. Data for patients who died before consenting were included in the final results as per a special section of the UK National Health Service Act. The trial received full nationwide ethics approval by three different national bodies. Despite the fact that patients were indeed randomized prior to consenting, several features of the study make concerns about "unethical experimentation" largely dismissible:

(a) The drugs used were two approved anticoagulants, used for their licensed indication, in the currently recommended doses, and are in routine use throughout the world.
(b) Patients presenting with an acute myocardial infarction are in pain, are being rushed to the cath lab, and maybe under the effect of drugs that cloud their judgment/consciousness (e.g. morphine). It is doubtful that a proper informed consent can be obtained under such circumstances.
(c) Reducing door-to-device times remains one of the most important goals of treatment in PPCI. The mean door-to-device time in HEAT-PPCI was 29 minutes and the investigators reported that randomization was done in less than 9 minutes. The value of a consent "squeezed" during that time frame is questionable.

In conclusion, the "delayed consent" model does sound plausible in limited scenarios when certain patient-, disease-, and treatment-specific features render prospective consenting unreasonable.

WHAT HAVE WE LEARNED?

HEAT-PPCI strongly challenges the currently perceived superiority of bivalirudin over UFH in patients undergoing PPCI. When GPIIb/IIIa inhibitors are used selectively, the risk of bleeding with UFH is not higher than that with bivalirudin, but the use of UFH is associated with significantly less stent thrombosis events. At a minor fraction of bivalirudin's cost, this is a welcome win for "plain old" UFH. In light of the currently available data, the clinical- and cost-effectiveness of bivalirudin in PPCI is not well established and the existing recommendations should be revised.

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