Editorial

Interventional Cardiology

to

HEAT-PPCI: fair criticism or resistance to change?

"When we do not know which therapy is best, one could almost argue that it is philosophically unethical not to include patients in a clinical trial."

Keywords: bivalirudin • clinical trials • heparin • medical ethics • PCI

The late breaking clinical trials sessions often represent the highlight of each of the major Cardiology meetings. It is here that for the first time much anticipated results of large and potentially practice-changing clinical trials are first released. These sessions are widely covered in the medical press and generate much debate. However, the recent presentation of the HEAT-PPCI trial during a late breaking clinical trial session at the 2014 ACC meeting generated more controversy than any in recent memory. The furore generated brought into question possible conflicts of interests of the chairing panelists and accusations of bullying toward the fellow who presented the trial. The reason for the storm generated was based on several unique aspects of the study design but also the (largely unfounded) belief that the results were in conflict with other randomized data in the same area.

HEAT-PPCI was an open-label single-center randomized control trial of antithrombotic therapy in ST elevation acute coronary syndrome (STE-ACS). Patients presenting for emergency angiography and STE-ACS were consecutively randomized in a 1:1 ratio to heparin or bivalirudin antithrombotic therapy. The primary efficacy outcome was a composite of all-cause mortality, cerebrovascular accident, reinfarction or unplanned target lesion revascularization at 28 days. The incidence of major bleeding was the main safety outcome measure. One thousand eight hundred and twenty-nine patients were enrolled in under 2 years, nearly all of whom (1812 patients) were included in the final analysis. The primary composite outcome occurred in 79 (8.7%) of 905 patients in the bivalirudin group and 52 (5.7%) of 907 patients in the heparin group (absolute risk difference 3.0%; relative risk 1.52, 95% CI: 1.09–2.13, p = 0.01). There was no difference in the rates of major bleeding, which occurred in 32 (3.5%) of 905 patients in the bivalirudin group and 28 (3.1%) of 907 patients in the heparin group (0.4%; 1.15, 0.70–1·89, p = 0.59) [1].

The panels at international meetings are generally made up of highly regarded and respected opinion leaders in their field. By facilitating intelligent academic discussion, highlighting the salient points and providing constructive criticism of the trial design, methodology and conduct, the panelists usually provide a balanced perspective on the presentations. Proceedings after the HEAT-PPCI presentation took a slightly different course. The presenter, Dr Shazad (the first author of the paper and at the time, a cardiology fellow) was rigorously questioned and not always afforded an opportunity to respond to panelist statements. The style of questioning was sufficiently unusual to have led some to describe it as 'at best patronizing but at worst bullying in nature' [2]. While the reasons for this relatively hostile reception are uncertain, what was clear is that the trial has sparked healthy debate and discussion at the ACC sessions and beyond.

Choice of comparator

One of the notable comments from an ACC panelist was that the results of HEAT-PPCI were 'markedly different' from other randomized trials in this area. We would argue

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that this statement is incorrect. The reason for this lies with the choice of comparator [2].

Fundamental to the design stage of any clinical trial is the selection of an appropriate comparator arm. This could be placebo or a pharmacologically active agent. The choice affects the inferences that can be made, the generalizability and the scientific acceptability of the results. For diseases or indications with well-established treatments, the current standard of care should be used in comparison with the novel agent.

In HORIZONS-AMI [3], the landmark trial establishing the use of bivalirudin in the STE-ACS, bivalirudin monotherapy was compared with the combination of unfractionated heparin (UFH) in combination with a glycoprotein IIb/IIIa inhibitor. Can GPIIb/IIIa inhibitors be considered a standard of care for primary PPCI and hence an appropriate comparator? Heparin has been established and used as antithrombotic therapy in ACS for many years, however its benefit was predominantly demonstrated in the pre-PCI era [4,5]. Despite this it has been used as the control arm in many clinical trials investigating new agents and is an accepted standard of care for PCI in most stable and acute settings.

GPIIb/IIIa inhibitors have potent anti-ischemic properties; however this consistently comes at the cost of an increase in bleeding events. Additionally there is a strong relationship with early bleeding complications associated with PCI and long-term mortality. This increased bleeding rate with GPIIb/IIIa inhibitors offsets the anti-ischemic benefits in all but the highest risk patients [6]. As a result, major clinical guidelines have never mandated the use of GPIIb/IIIa inhibitors in primary PCI but rather advocated their use in those patients with large thrombus burden or inadequate antiplatelet loading [7,8]. It is possible that the latter is a diminishing problem since the advent of the newer generation of oral antiplatelet drugs such as Ticagrelor and Prasugrel. With this in mind, one can argue that UFH in combination with glycoprotein IIb/IIIa inhibitor is not the standard of care for primary PCI in STE-ACS and therefore was not a suitable choice of comparator in HORIZONS-AMI.

In addition, over 65% of those patients randomized to bivalirudin monotherpay in HORIZONS-AMI received UFH prior to bivalirudin administration. Therefore, prior to HEAT-PPCI, a genuine comparison of heparin monotherapy and bivalirudin monotherapy had not been carried out.

Single versus multicenter

The achievement of enrolling nearly 2000 patients to a single trial in a single center in under 1 year is nothing short of extraordinary. Yet in the modern era of 'mega-trials,' this is extremely unusual. So how do we interpret the results of single-center trials? Are they as robust and as valid as multicenter trials? In answering these questions it is both the internal and external validity that must be considered.

Internal validity is the extent to which observed treatment effects can be ascribed to differences in treatment and not confounding or bias, thereby allowing the inference of causality to be ascribed to a treatment. The use of randomization in HEAT-PCI minimized the chance of confounding or allocation bias by investigators. The open-label design is a potential source of bias. It is possible that the knowledge of treatment group may have led to biased assessment of trial end points. This may be of particular importance in a single-center trial where investigators have been involved with the clinical trial from the very early stages and could have vested interests in the outcome. HEAT-PPCI was designed to minimize the chances of adjudication bias by the appointment of an independent Clinical Events Committee (using predefined definitions) who assessed all primary, safety and stent thrombosis endpoints.

It is the external validity or generalizability of single-centered trials that often comes into question. In assessing generalizability it is important to carefully consider the inclusion and exclusion criteria, demographics of recruited patients, reasons for not enrolling eligible patients and differing medical practices between centers/nations. The HEAT-PPCI investigators have done a remarkable job in designing a pragmatic, real-world trial, by minimizing the exclusion criteria. The investigators worked under the principle 'every patient, every time' to ensure that all eligible patients were enrolled. As a result, 1829 patients were randomized in less than 2 years. This is in contrast to most cardiovascular trials where tight inclusion and exclusion criteria often exclude those patients at highest risk and the failure to enroll all eligible patients leads to the underrepresentation of the elderly, females and patients from low socioeconomic status.

Does medical management of STE-ACS in HEAT-PPCI reflect practice across the rest of the world? Radial access was used in over 80% of patients, ticagrelor or prasugrel in nearly 90% [1]. This is higher than in previous trials of bivalirudin but is likely reflective of evolving practices across the developed world. Heparin was dosed in line with European guidelines [9] and bivalirudin was dosed within its licensed dose. HEAT-PPCI is therefore a good reflection of the modern management of primary PPCI. A major limitation to the generalizability of HEAT-PPCI is that the enrolled population was 95% Caucasian and therefore the results should be applied with caution when man-

aging patients from other ethnic backgrounds. This is highlighted by the recently presented and currently unpublished BRIGHT trial.

BRIGHT was a multicenter randomized controlled trial of 2194 patients recruited from 82 Chinese centers. Patients were randomized to bivalirudin, heparin alone or heparin in combination with the GPIIb/IIIa inhibitor tirofiban. The primary endpoint was 30-day net adverse clinical event. In contrast to the results of HEAT-PPCI there was a significant reduction in NACE in the bivalirudin group compared with the heparin monotherapy group (8.8% vs 13.1, p = 0.045), with significantly more bleeds in the heparin arm and no difference was seen in MACE. No difference in the rates of stent thrombosis was seen between treatment groups. These discordant results may be a result of ethnic differences leading to an altered pharmacodynamic response or subtle differences in trial methodology. Patients in BRIGHT received higher doses of heparin compared with HEAT-PPCI (100U/kg compared with 70U/kg) and also a prolonged bivalirudin infusion post PCI. What is clear is that there seems to be no consensus on the optimum doses of heparin or bivalirudin in the setting of primary PCI.

Delayed consent

The process of delayed consent used in HEAT-PPCI, more than any other aspect of the trial, has generated controversy and debate and forms the subject of an editorial in the Lancet [2,7]. The criticisms center on whether it is ethical to not seek consent from a conscious patient prior to randomization. This goes against previous practice in the STEMI arena.

Informed consent is an essential message enshrined in all modern ethical codes of practice governing biomedical research. The Council for the International Organization of Medical Research state that for informed consent to be valid the individual must be competent; have received the necessary information; have adequately understood the information; have time to consider the information; arrive at a decision with undue coercion, inducement or intimidation [8]. Is it possible for someone presenting with a STEMI scheduled for primary PPCI to fulfill these criteria?

Patients are invariably in pain, distressed and often have been given opiates to relieve their symptoms; as such they may not be competent to make a decision. The pressing urgency not to delay revascularization will compromise the time available to give the patient the necessary information and check their understanding to make a decision. Patients aware of the significant mortality associated with their condition who have placed their lives in the hands on the operating cardiologist and also asked to participate in research by the same physician are likely to feel an obligation to participate. Is this a form of coercion? Overall there is a very strong argument that it is not possible to fulfill all the criteria required for valid consent in the setting of STE-ACS research and as a result not using a process of delayed consent in previous STE-ACS could be regarded as unethical.

Prior to HEAT-PPCI there had been no direct head to head comparison of bivalirudin and heparin in primary PCI although both treatments are licensed for this indication and therefore are assumed to have clinical equipoise. When we do not know which therapy is best, one could almost argue that it is philosophically unethical not to include patients in a clinical trial. Not performing and enrolling patients into important studies delays scientific progress and potentially harms patients. Based on the inability to adequately consent patients in the throes of a STE-ACS and the clinical equipoise of the two treatments both used under licensed indications we believe the trial consent to not only be ethical but highly innovative and the investigators should be commended for their achievement.

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