Editorial

Interventional Cardiology

Anticoagulants in an acute myocardial infarction: should we adopt a 'back to the future' strategy?

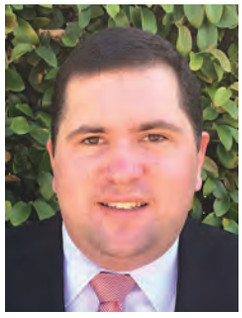
"Our approach is to consider heparin as the default agent of choice in the vast majority of ST-elevation myocardial infarction cases."

Keywords: acute myocardial infarction • anticoagulants • bivalirudin • heparin

Acute myocardial infarctions present a unique set of clinical and technical challenges, which must be dealt with in a timely manner. Choosing the proper anticoagulation agent is paramount in the treatment paradigm for achieving clinical success. Unfractionated heparin and bivalirudin are far and away the two agents most preferred by operators throughout the USA and Europe. Multiple, large, well-designed, randomized clinical trials such as the HORIZONS-AMI trial, the EUROMAX trial and the HEAT-PPCI trial have articulated the clinical variations between the two agents and have attempted to elucidate the superior agent in terms of safety and efficacy.

Bivalirudin and heparin both enjoy American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) class I recommendations as anticoagulant therapy, which may be considered to support percutaneous coronary intervention of the infract-related vessel [1,2]. While the use of heparin commits operators to routine checking of activated clotting times (ACT) to maintain therapeutic levels, bivalirudin does not necessitate the need to adjust the dose base on the ACT. In the HORIZONS-AMI trial, although ACT was checked in the bivalirudin arm, the protocol did not call for readjusting the dose based on the results [3,4]. Worrying about one less variable helps the operator focus better at the task at hand.

Despite its relative ease of use, bivalirudin became a blockbuster drug for the interventional cardiologist because it was shown to be as efficacious and possibly safer than heparin plus, a glycoprotein IIb/IIIa inhibitor. An informed debate about which drug is superior cannot be had without discussing glycoprotein IIb/IIIa inhibitors. In HORIZONS-AMI, bivalirudin was directly compared with heparin in addition to a IIb/IIIa inhibitor [3]. EUROMAX was billed as a trial where glycoprotein inhibitor use was optional. However, 69.1% of patients in the heparin arm received a IIb/IIIa inhibitor while only 11.5% of patients receiving bivalirudin were treated with a IIb/IIIa inhibitor. The study's results were congruent with HORIZONS-AMI in the fact that it demonstrated that primary outcome of death or noncoronary artery bypass graft-related major bleeding was higher in the heparin-treated arm [5]. HEAT-PPCI was a single-center, randomized trial that compared bivalirudin to heparin directly. It demonstrated that heparin had a lower composite efficacy end point at 28 days, which was defined as all-cause mortality, cerebrovascular accident, reinfarction or additional unplanned target lesion revascularizations (bivalirudin 8.7% vs heparin 5.7%; $p = 0.01$). This was primarily driven by a lower incidence of new myocardial infarctions and additional unplanned target vessel revascularizations. In addition, the primary safety end point of major bleeding at 28 days was demonstrated to not be statistically different (bivalirudin 3.5% vs heparin 3.1%; $p = 0.59$) [6]. Most operators accept that IIb/IIIa inhibitors increase the rate of bleeding. HEAT-PPCI demonstrated that when compared head to head, heparin may be more efficacious and more importantly, did



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not increase the incidence of major bleeding events as previous studies suggested.

While major bleeding is a serious problem, stent thrombosis is a greater calamity. The incidence of stent thrombosis was higher in the bivalirudin-treated arms versus the heparin-treated arms in all studies. Of note, however, the rate of occurrence of stent thrombosis was strikingly higher in the HEAT-PPCI trial as compared with the HORIZONS-AMI trial (HEAT-PPCI: bivalirudin 3.4% vs heparin 0.9%, p = 0.001; HORIZONS-AMI: definite stent thrombosis: bivalirudin 2.2% vs heparin 1.4%, p = 0.09, acute stent thrombosis [<24 h] bivalirudin 1.3% vs heparin 0.3%, p < 0.001) [3,6]. This may be a result of HEAT-PPCI being a single-center study or due to the total duration of time bivalirudin was continued after the completion of the intervention.

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In addition, it is important to note that the majority of the patients in HEAT-PPCI were treated via a transradial approach while in HORIZONS-AMI the femoral artery was the access site of choice [6,7]. Such a variation deserves significant attention as the vast majority of interventions in interventional cardiology currently are done via the transfemoral approach. Historically, however, femoral access has been associated with an increased rate of vascular and bleeding complications as compared with a transradial method irrespective of antiplatelet or anticoagulant used [8]. In regards to the choice of anticoagulants used during acute myocardial infarctions, different anticoagulants may be better suited with different methods of access.

In a situation where minimizing the time from symptom onset to achieving coronary reperfusion is the principal objective, a patient's comprehensive medical history and laboratory data are not always readily available when the decision is made to take the patient to the catheterization laboratory. Such circumstances favor a medication that does not need to be adjusted based on a patient's creatinine clearance, such as heparin.

Finally, the HEAT-PPCI trial is the only randomized, prospective study to date comparing bivalirudin to heparin in the setting of percutaneous coronary interventions for acute ST-elevation myocardial infarctions. Therefore, some have postulated that its conclusions need to be viewed with more scrutiny given that multiple previous trials had more favorable results for bivalirudin. However, a recent meta-analysis in the journal *Lancet* that looked at 16 trials comparing the two medications in various clinical scenarios, including ST-elevation myocardial infractions, bolsters the findings demonstrated in HEAT-PPCI. It confirmed that when the two agents were compared, there was an increased rate of recurrent myocardial infarction, stent thrombosis and target vessel revascularization with bivalirudin. Furthermore, the lower bleeding rate correlated directly with the concurrent use of IIb/IIIa inhibitors [9].

The field of interventional cardiology is in an ever-evolving state. The risks and benefits of proposed medical therapies are tested, scrutinized and further prodded. In terms of the anticoagulant of choice in the catheterization laboratory during an acute ST-elevation myocardial infarction, heparin has stood the test of time. However, bivalirudin cannot be designated as a relic of tried and forgotten therapies. Although the naysayers of bivalirudin have called for a 'back to the future' strategy to be uniformly adopted, a more pragmatic approach should be entertained. Our approach is to consider heparin as the default agent of choice in the vast majority of ST-elevation myocardial infarction cases. Bivalirudin should be considered when adding a IIb/IIIa inhibitor to heparin is likely or if the patient's bleeding risk is high, especially if femoral access is used. Until new data are available, if bivalirudin is chosen we recommend the concomitant use of newer, more potent antiplatelet medications, rebolusing if the ACT is lower than 225 and continuing bivalirudin infusion for 30–45 min after the conclusion of the case.

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