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Review Article

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Clinical Outcome of Patients of Acute Coronary Syndrome at 7 and 30 days Undergoing Percutaneous Coronary Interventions and Treated with Bivalirudin and Heparin

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ABSTRACT

Background: Recent data suggest that Bivalirudin provides ischemic protection superior to Heparin,and comparable to Heparin plus glycoprotein IIb/IIIa inhibitors, with significantly fewer bleeding complications. Whetherthis advantage persists in large population has not beenfully defined.

Objective: This study systematically evaluates clinical outcomes of treatment with Bivalirudinvs Heparin in patients of acute coronary syndrome undergoing Percutaneous coronary interventions (PCI).

Methods: We analyzed prospective, randomized controlled trials via electronic searches that have reported clinical outcomes at 7 and 30 days. The outcomes were major bleeding, net clinical outcomes and Major Adverse Cardiac Events – MACE. Data from individual trials were combined by a meta analysis method of Mantel-Haenszelcalculate a relative risk (RR) and 95% confidence interval (95%CI) across the studies.Theheterogeneity across the trials was assessed through χ^2 statistic, I^2 andvisual inspection of the forest plots.

Results: This meta-analysis involved a total of 30,088 patients (Bivalirudin, n=15,105; Heparin, n=14,983). Compared with Heparin, Bivalirudin was associated with a lower risk of major bleeding (RR 0.38; 95%CI 0.29-0.48 at 7 days and RR 0.67;95%CI 0.60-0.75 at 30 days), net clinical outcomes (RR 0.56; 95%CI 0.47-0.66 at 7 days and RR 0.89; 95%CI 0.83-0.96 at 30 days) and MACE (RR 0.78; 95%CI 0.63-0.96 at 7 days). There was no significant difference in case of MACE at 30 days (RR 1.02; 95%CI 0.93-1.11). Heterogeneity was observed across the trials that reported major bleeding (χ^2=14.71, 5 df, p=0.01, I^2=66%) at 30 days, but not at 7 days for reported major bleeding, and also for net clinical outcomes and MACE both at 7 days and 30 days.

Conclusion: This analysis further supports that Bivalirudin provides significantimprovement in net clinical outcomes and MACE with a significant reduction of bleedingcomplications.

KEYWORDS *Major bleeding, Net clinical outcomes, MACE, Bivalirudin, Heparin*

Introduction

Bivalirudin is most widely used direct thrombin inhibitor all over the world, which reduce the risk of major adverse cardiac events (MACE) and major bleeding as reported in various clinical studies. Besides its property to dissolve the fibrin bound thrombin, Bivalirudin also shows predictable linear pharmacokinetics and avoidance of (Heparin induced) thrombocytopenia. Early trials of Bivalirudin as an anticoagulant suggested similar endpoints as those of Heparin with GP IIb/IIIa inhibitors with lower rates of major bleeding. Our aim was to detect a clinically meaningful dif-

ference in outcomes by performing a meta-analysis of most available published clinical studies of Bivalirudin in acute cardiac syndromes (ACS).

Materials and Methods

To the best of our knowledge, this meta-analysis includes all the currently completed randomized published trials that have compared different outcomes with Bivalirudin vs. Heparin in patients of ACS who underwent PCI. This analysis used the end points of death, post procedural myocardial infarction (MI), urgent revascularization, and bleeding as defined within each clinical trial. Specifically, three outcomes at 7 and 30 days, e.g. Major bleeding, Net Clinical Outcomes (Death, MI, Revascularization and Major bleed) and Major Adverse cardiac events (MACE) were considered for comparison.

Search strategies included an electronic search of bibliographic databases (PubMed, Medline and Science Direct), specific journals (Journal of Invasive cardiology, New England Journal of Medicine, Circulation, American Heart Journal, American Journal of Cardiology, Journal of American Medical Association, Journal of the American College of Cardiology), and review of bibliography from eligible trials and use of the "See Related Articles" links.

As mentioned, the outcomes were the combined incidence of death from any cause, myocardial infarction, or urgent target-vessel revascularization (MACE) and major bleeding. This triple end point (MACE) was aimed at assessing the risk of ischemic complications. Net clinical outcome was intended to measure the risk of both ischemic (MACE) and bleeding complications and was the basis for determining the net clinical benefit. Myocardial infarction (MI) was defined as the development of pathologic Q waves (≥30 msec in duration and ≥0.1 mV in depth) in two or more contiguous electrocardiographic leads or an elevation of creatine kinase MB isoenzyme levels (or total creatine kinase if measures of creatine kinase MB were not available) to at least two times the upper limit of the normal range. Urgent revascularization was defined as severe myocardial infarction requiring immediate surgery or PCI. The definition of major bleeding was intracranial, intraocular, or retroperitoneal haemorrhage; clinically overt blood loss resulting in a decrease in haemoglobin of more than 3 g per deciliter; any decrease in haemoglobin of more than 4 g per decilitre; or transfusion of 2 or more units of packed red cells or whole blood.

Two authors (AK and RK) separately reviewed literature search to identify studies that are randomized controlled trials evaluating outcomes at 7 and 30 days with Bivalirudinvs Heparin in patients of acute coronary syndrome undergoing percutaneous coronary interventions (PCI). Any disagreement in the rejection process was first handled between them. When this could not be done, a third independent reviewer's opinion was sought. Studies published in languages other than English and studies with outcome reported on other than 7 or 30 days were excluded.

Statistical Analysis

Meta-analysis (i.e, statistical pooled results) for major bleeding, MACE and Net Clinical outcome was performed using the Mantel-Haenszel method. All three outcomes were analyzed as dichotomous variables using fixed-effect model to calculate a weighted estimate (risk ratio) and 95% confidence interval (CI) across the studies. The heterogeneity across the trials was assessed through a χ^2 statistic, degree of freedom (P value of 0.10 was used to determine statistical significance), I^2 and visual inspection of the forest plots. I^2 value represents the percentage of the total variation across trials due to heterogeneity rather than chance (I^2 value <25% is low and >75% is high). All analyses were done using RevMan 5 (Cochrane Collaboration).

Results

The literature search identified 2 studies (BAT and CAHET D1+D2) that reported outcomes at 7 days and 5 (ACUITY PCI, HORIZONE AMI, ISAR REACT 3, REPLACE 1 and REPLACE 2) studies that reported outcomes at 30 days, involving a total of 30,088 patients (Bivalirudin, n = 15 105; Heparin, n = 14 983), met our inclusion criteria. Detail flow chart for inclusion of studies is shown in Figure 1. Out of these 30,088 patients, 4520 patients (Bivalirudin, n = 2305; Heparin, n = 2215) of 2 trials that reported outcomes at 7 days and 25568 patients (Bivalirudin, n = 12800; Heparin, n = 12768) of 5 trials that reported outcomes at 30 days were included in this Meta analysis. All the included studies characteristics are mentioned in Table 1. ACUITY PCI study was divided into 2 subpart; ACUITY PCI 1 (Bivalirudin + GPIIb/IIIa inhibitor) and ACUITY PCI 2 (Bivalirudin alone) in comparison of Heparin plus GP IIb/IIIa inhibitor. All the seven included trials had reported required outcomes e.g. major bleeding, net clinical outcomes (death, MI, revascularization and major bleed) and MACE.

Major bleeding was reported in all the 7 identified studies as shown in Figure 2. Statistically significant difference was observed for major bleeding with a RR of 0.38 (95% CI 0.29 to 0.48) at 7 days (Figure 2A) and RR of 0.67 (95% CI 0.60 to 0.75) at 30 days (Figure 2B) indicates low incidence of bleeding with Bivalirudin. There was no heterogeneity across the trials that reported Major bleeding at 7 days (χ^2=0.39, 1 df, p=0.53, I^2 =0%) but observed across the trials that reported major bleeding at 30 days (χ^2=14.71, 5 df, p=0.01, I^2 =66%).

Figure 3 shows the net clinical outcomes at 7 days (Figure 3A) and at 30 days (Figure 3B). Net clinical outcomes were significantly lower in Bivalirudin group with RR of of 0.56 (95% CI 0.47 to 0.66) at 7 days and RR of 0.89 (95% CI 0.83

to 0.96) at 30 days. Heterogeneity was not observed across the trials that reported net clinical outcomes at 7 days (χ^2=2.37, 1 df, p=0.12, I^2 =58%) and at 30 days (χ^2=3.63, 5 df, p=0.60, I^2 =0%) as well.

Analyzed results of ischemic triplet (MACE), as shown in Figure 4, revealed statistically significant difference observed at 7 days with RR of 0.78 (95% CI 0.63 to

Table 1. Characteristics of included studies

Name of the Study	Year	Indication	Dose of Bivaluridin	Use of GPIIb/IIIa	Dose of UFH	Use of GPIIb/IIIa
ACUTY PCI 1	2007	Moderate to High risk ACS	0.75 mg/kg	100%	140 U/kg	100%
ACUTY PCI 2	2007	Moderate to High risk ACS	0.75 mg/kg	Not Given	140 U/kg	100%
HORIZONE AMI	2008	STEMI	0.75 mg/kg	7%	70 U/kg	100%
ISAR REACT 3	2008	Unstable Angina/NSTEMI	0.75 mg/kg	7%	70 U/kg	100%
REPLACE 1	2004	Unstable Angina/NSTEMI	0.75 mg/kg	PID	70 U/kg	PID
REPLACE 2	2003	Unstable Angina/NSTEMI	0.75 mg/kg	7.20%	140 U/kg	100%
BAT	2001	Unstable Angina/NSTEMI	1.0 mg/kg	Not Given	175 U/kg	15 U/Kg infusion for 18-2 hours
CACHET D1+D2	2002	Unstable Angina	0.50 mg/kg followed by 1.75 mg/kg & 0.75 mg/kg	-	70 U/kg	100%

[1]ACUITY PCI = Acute Catheterization and Urgent Intervention Triage Strategy; [2]HORIZONE AMI= Bivalirudin during primary PCI in acute myocardial infarction; [3]ISAR-REACT 3= The investigators who participated in the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment; [4]REPLACE-1 =Comparison of Bivalirudin vs Heparin During Percutaneous Coronary Intervention (the Randomized Evaluation of PCI Linking Angiomax to Reduce Clinical Events); [5]REPLACE-2 =Long-term Efficacy of Bivalirudin and Provisional Glycoprotein IIb/IIIa Blockade vs Heparin and Planned Glycoprotein IIb/IIIa Blockade During Percutaneous Coronary Revascularization; [6]BAT = Bivalirudin Angioplasty Trial; [7]CACHET = Comparison of Abciximab Complications with Hirulog for CVE Trial. STEMI: ST- segment elevation myocardial infarction; NSTEMI: Non ST- segment elevation myocardial infarction ;

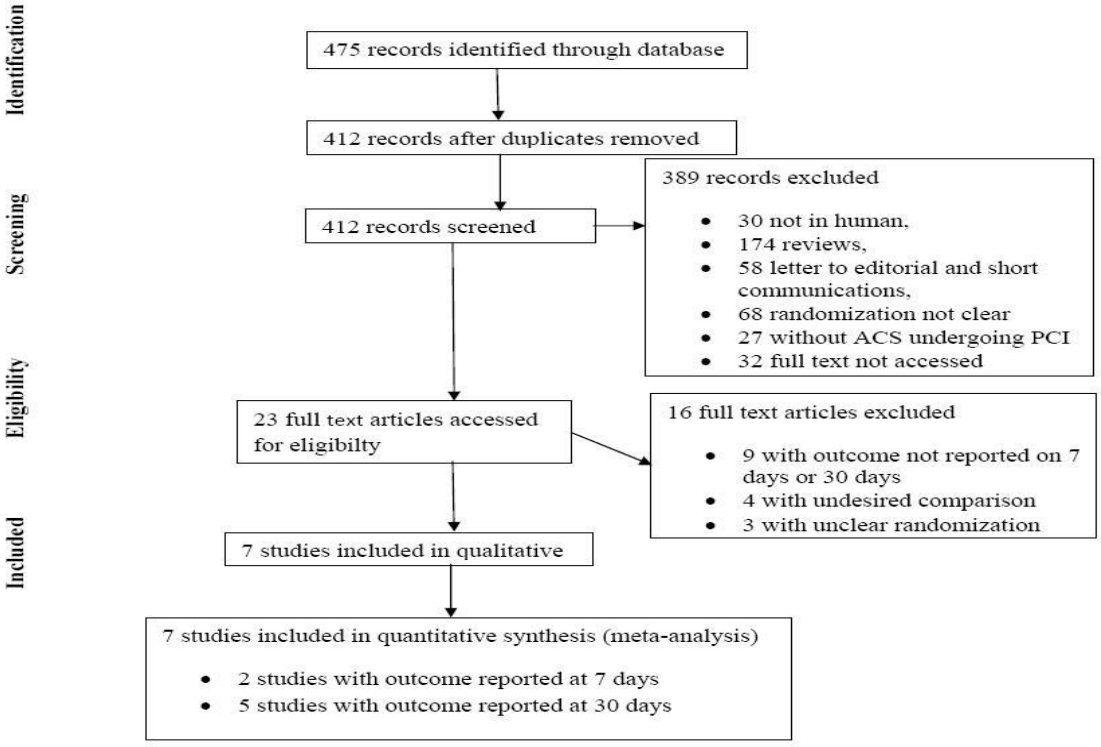


Figure 1. Flowchart of included studies for meta-analysis

0.96) but not at 30 days with RR of 1.02 (95% CI 0.93 to 1.11). No significant heterogeneity was observed across the trials that reported MACE either at 7 days (χ^2=1.47, 1 df, p=0.22, I^2 =32%) or at 30 days (χ^2=5.24, 5 df, p=0.39, I^2 =05%).

Discussion

More than 1.4 million persons are admitted to hospitals in the United States every year with acute coronary syndromes (e.g., unstable angina or myocardial infarction without ST-segment elevation).[8]In India, an estimated 2 million patients are currently suffering from coronary heart diseases also making it the country with highest acute syn-

dromes in the world.[9] The thrombotic complications in patients of acute coronary syndrome (ACS) undergoingpercutaneous coronary interventions are related to activation of the intrinsic coagulation system and to platelet aggregation. During coronary interventions, Heparin has been the primary choice for anticoagulation since its inception.[10] Aspirin, clopidogrel – a platelet glycoprotein IIb/IIIa inhibitor, and an antithrombotic agent are also recommended for patients for whom an invasive strategy is chosen.[11-13]

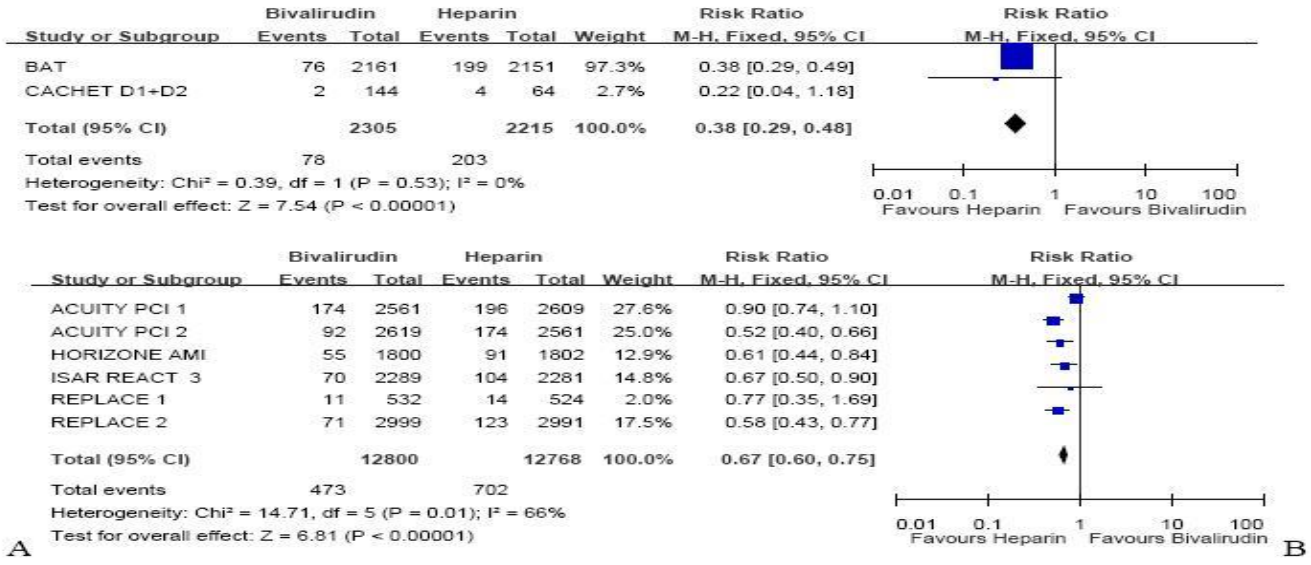


Figure 2. Major bleeding **A** at 7 days and **B** at 30 days

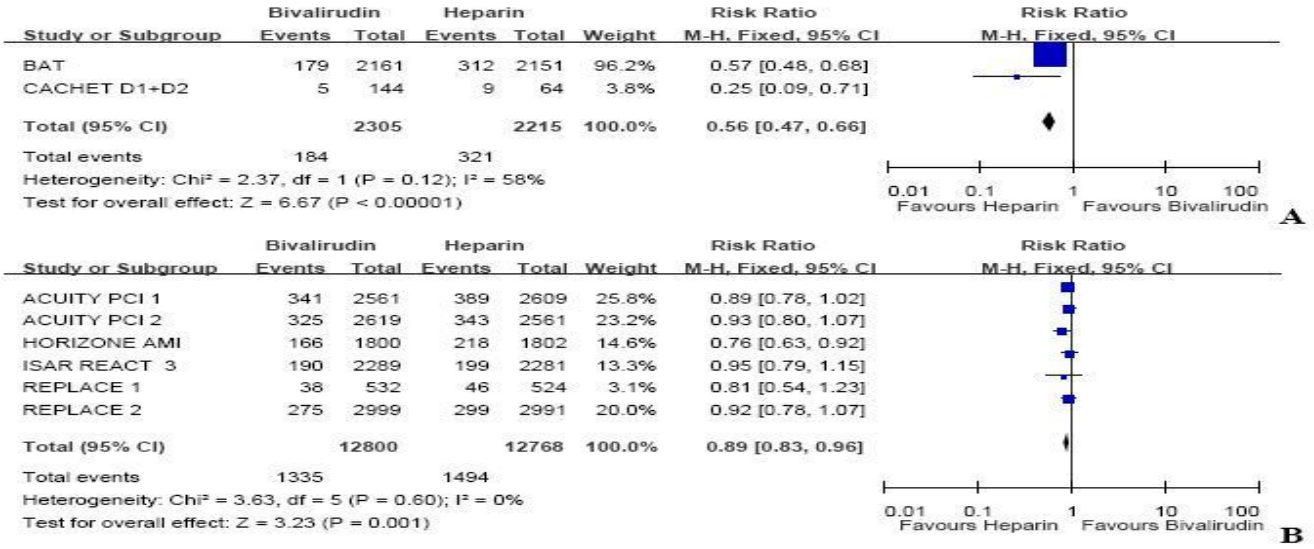
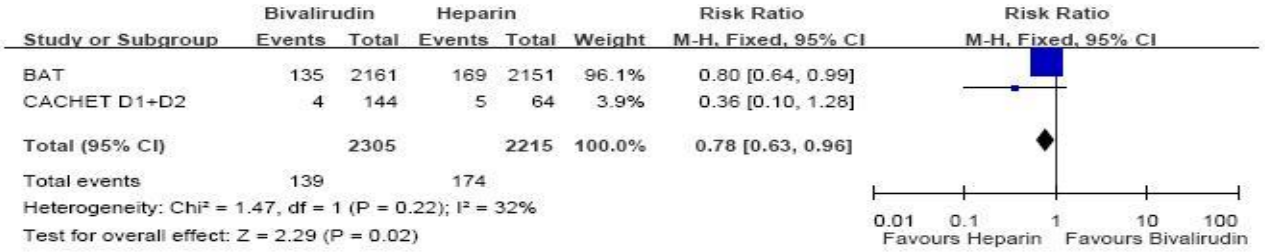


Figure 3. Net Clinical Outcomes **A** at 7 days and **B** at 30 days.

Unfractionated Heparin has been the standard of adjunctive antithrombin therapy during percutaneous coronary intervention (PCI) for more than 25 years. Yet Heparin is subject to important intrinsic limitations, including unpredictable pharmacokinetics, inhibition by plasma proteins, and the potential to activate platelets.[14-17] Considerable reductions in periprocedural complications have been achieved with administration of glycoprotein IIb/IIIa (GpIIb/IIIa) antagonists in addition to Heparin.[18] These potent platelet inhibitors are not used universally because of cost and increased bleeding risk. Most of the anticoagulants are not capable to dissolve the fibrin bound thrombin. Such thrombin usually activates platelets through thromboxen A2 independent mechanism which can not be blocked by aspirin or any other anticoagulants except direct thrombin inhibitors (DTI). One of the best available DTI, with well established safety and efficacy in various indication of ACS is Bivalirudin.

This meta analysis of 7 trials reveals a lower risk of major bleeding with Bivalirudin in comparison to Heparin in patients of ACS undergoing PCI. Statistically significant improvement is suggested with Bivalirudin treatment in net clinical outcomes at both 7 and 30 days. The ischemic events (MACE) are higher in Heparin group at 7 days but at 30 days there is no significant difference between the two groups. All 7 trials included in the meta analysis consisted of homogeneous population as there is no significant heterogeneity found between Heparin and Bivalirudin groups except in the case of major bleeding at 30 days and that is because of diference in doses and GP IIb/IIIa inhibitor use among the 5 trials.

This meta-analysis shows a significant reduction in both ischemic events as well as major bleeding, contrastingameta-analysis performed by Kong and his colleagues[19] which included 6 trials with 5674 patients. [20, 21-23, 24] The latter showed thatBivalirudinreduces the incidence of ischemic heart disease at least to the same degree as does UFH (Unfractionated Heparin) but with statistically significant reduction inmajor bleeding (P < .001). Another meta-analysis performed by Singh et al.[25] has reported similar results to ours but they pooled data from trials that reported outcomes at different time period ranging from 48 hours to 6 months. We have combined the data from the trials that reported outcomes specifically at 7 days and 30 days separately which is more logical. The combination of both safety and efficacy measures is not ideal, hence we reported safety (major bleeding and ischemic event and net clinical outcomes) separately from the efficacy measures.



A

B

Figure 4. Major Adverse Cardiac Event (MACE) **A** at 7 days and **B** at 30 days.

Conclusion

This meta-analysis finds that Bivalirudin is associated with lower incidences of net clinical outcomes as well as bleeding at 7 days and 30 days relative to those of Heparin. Furthermore, Bivalirudin treatment showed a lower risk of ischemic event (MACE) at 7 days than that of Heparin but at 30 days there was no significant difference between Heparin and Bivalirudin treated groups.

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