

Bivalirudin Vs Heparin with Glycoprotein IIB/IIIA Blockade in Acute Coronary Syndrome (ACS) Patients Undergoing Percutaneous Coronary Revascularization: An Observational Study in Indian Patients

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ABSTRACT

Introduction: Currently either heparin or bivalirudin can be used during PCI as a class I indication as per PCI guidelines published by AHA in 2011. There are multiple randomized control trials e.g. HORIZONS-AMI, EUROMAX, REPLACE 2, ISAR-REACT 3, ACUITY which favors bivalirudin when compared with heparin in different clinical situations, but the role of bivalirudin during PCI has also been questioned in a recent large, open label randomized control trial, HEAT PPCI which showed higher incidence of acute stent thrombosis and significant bleeding in bivalirudin arm. Present study designed to observe clinical outcomes and adverse events for 30 days in post PCI patients.

Material and Methods: A total of 124 patients were studied over a period of 6 months (May 2015-November 2015). Out of 124 patients, 61 received heparin with provisional planned glycoprotein IIB/IIIA (GPI) blockade and 63 received bivalirudin with provisional planned glycoprotein IIB/IIIA blockade. Baseline characteristics of the patients were well matched. Pre procedure aspirin and P2Y12 inhibitor was given to all patients. Glycoprotein IIB/IIIA inhibitor was given in 34.4% of patients in heparin group. No patient in the bivalirudin group received glycoprotein IIB/IIIA inhibitor. Main route of access was femoral (95.9%). Single vessel disease was seen in 70.96% of patients.

Results: At time of discharge, MACE was observed in the two cases in the bivalirudin group (3.2%) while heparin group showed no MACE. Both MACE were attributed to mortalities. Major bleeding was seen in only one patient who received bivalirudin (1.6%). No case of cerebrovascular accident, re-infarction or unplanned target lesion, revascularization was observed in either group at time of discharge. At 30 days, one additional MACE happened in the form of definitive sub acute stent thrombosis in bivalirudin arm with no addition in heparin group. Total MACE at 30 days was 4.7% in bivalirudin group, while no MACE was observed in the heparin group. At 30 days, no additional major bleeding noted in any of the arm.

Conclusion: In this study we could not find any statistically significant difference in 30 days efficacy and safety outcome in two groups, one receiving bivalirudin with provisional planned glycoprotein IIB/IIIA blockade and other heparin with provisional planned glycoprotein IIB/IIIA blockade. Though there were 3 MACE and 1 major bleed in bivalirudin arm comparing with no such event in heparin arm but this difference was not statistically significant.

Keywords: Acute Coronary Syndrome, Bivalirudin, Heparin, Percutaneous Coronary Intervention

INTRODUCTION

Acute coronary syndromes (ACS) are the major cause of death and disability worldwide. Though recent advancements in management of ACS has led to dramatic reduction in early and long-term mortality and morbidity, but still this is the most common cause of cardiovascular death in most parts of the world, including India. Unstable angina (UA), acute non-ST elevation myocardial infarction (NSTEMI), and acute ST elevation myocardial infarction (STEMI) are the three presentations of ACS. The reason for STEMI is the thrombotic occlusion of major epicardial coronary artery in the absence of adequate collaterals. Treatment is targeted to restore normal TIMI 3 coronary flow either by mechanical or chemical reperfusion. The preferred mode of treatment is mechanical reperfusion. It restores normal myocardial perfusion, reduces infarct size, preserves left ventricular function and has significant survival benefit marked in patients aged below 75 years, and presented within 6 hours of symptom onset. American College of Cardiology Foundation/American Heart Association guideline for the management of STEMI recommends use of primary percutaneous coronary intervention (primary PCI) for any patient with an acute STEMI who can undergo the procedure in a timely manner by persons skilled in the procedure. Mechanical revascularization by PCI even after 6 hours of initiation of myocardial infarction (MI) and up to 24 hours might improve left ventricular ejection fraction by preventing negative ventricular remodeling, infarct expansion, ventricular aneurysm formation, and risk of ventricular arrhythmia associated with ventricular dilatation.¹

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PCI itself has some limitations, as it results in iatrogenic plaque rupture that increases the risk for thrombosis and ischemic complications. The central role of thrombin in this process makes it an essential target for pharmacotherapy,² although the antithrombin regimen decreases the ischemic complications, but it is associated with increased risk of bleeding.³ The recent research on antithrombotic has focused on finding a balance between ischemic complications such as myocardial infarction (MI), stent thrombosis and catheter thrombosis vs. bleeding events such as major and minor bleeding, vascular access site bleeding and need for blood transfusion. Currently either heparin or bivalirudin can be used during PCI as a class I indication, as per PCI guidelines published by AHA in 2011.⁴ There are multiple randomized control trials eg. HORIZONS-AMI, EUROMAX, REPLACE 2, ISAR-REACT 3, ACUITY which favors bivalirudin use when compared with heparin in different clinical situations. But the role of bivalirudin during PCI has also been questioned in a recent large, open label randomized control trial. HEAT PPCI which showed higher incidence of acute stent thrombosis and significant bleeding in bivalirudin arm.⁵⁻¹⁰ The aim of the study was to observe clinical outcomes and adverse events for 30 days in post PCI patients who are admitted to Department of cardiology, Medanta over period of 6 months between May 2015-November 2015.

MATERIAL AND METHODS

The study population consist of patients with acute coronary syndrome who had already undergone percutaneous coronary intervention (PCI) conducted in the Department of Cardiology, Medanta.

A total of 124 patients were studied over a period of 6 months (May 2015-November 2015). Patients were divided into two categories. Category I (N=61) included the patients, who have received heparin with provisional planned

glycoprotein IIB/IIIA (GPI) blockade and in Category II (N=63) there were patients who have received bivalirudin with provisional planned glycoprotein IIB/IIIA blockade. The patients were treated for PCI as per European Society of Cardiology guidelines.¹¹ Pre procedure aspirin and P2Y12 inhibitor was given to all patients. Glycoprotein IIB/IIIA inhibitor was given in 34.4% of patients in heparin group. No patient in the bivalirudin group received glycoprotein IIB/IIIA inhibitor. Main route of access was femoral (95.9%). Single vessel disease was seen in 70.96% of patients. Left anterior descending artery was the most common vessel involved. Balloon angioplasty was done only in three patients in bivalirudin group, while in all others drug eluting stent was implanted. In bivalirudin group, 32 out of 63 patients were having TIMI flow 0 to 1 before undergoing the procedure, while in heparin group, 20 patients were having pre procedure TIMI flow 0 to 1. Post procedure, four patients in bivalirudin group had TIMI 2 flow as compared to one in heparin group. Metallic stent was implanted in 107 cases whereas 14 patients received Bioresorbable Vascular Scaffold (BVS). There was no associated adverse event in any of these patients.

Inclusion and exclusion criteria: Patients admitted with acute coronary syndrome with age more than 18 years and received aspirin and P2Y12 inhibitor pre PCI are included in study. Artificial ventilation before procedure and reduced conscious level or other factors precluding the administration of oral anti platelet therapy are excluded from study.

Outcome at discharge and at 30 days: Primary outcome at discharge and at 30days was measured as any major adverse cardiac event (MACE). MACE is a composite of all-cause mortality, cerebrovascular accident, reinfarction, or additional unplanned target lesion revascularization. Safety

	Heparin (N=61)	Bivalirudin (N=63)
Male sex - no. (%)	50 (82.0)	52 (82.5)
Age-yrs (Mean ± SD)	58.3±11.2	57.8±11.7
Weight-kg (Mean ± SD)	74.2±11.3	76.2±10.1
Diabetes- no. (%)	24 (39.3)	30 (47.6)
Hypertension- no. (%)	31(50.8)	32(50.8)
Family history- no. (%)	11 (18.0)	14 (22.2)
Current smoker- no. (%)	11 (18.0)	9 (14.3)
Previous MI- no. (%)	9 (14.89)	11 (17.5)
Previous PCI- no. (%)	8(13.1)	8 (12.7)
Previous CABG- no. (%)	1 (1.6)	2 (3.2)
Platelet count- x103/μl (Mean ± SD)	272.1±94.4	289.7±87.0
Hb- gm/dl (Mean ± SD)	13.7±1.9	13.4±1.9
Estimated glomerular filtration rate –ml/min (Mean ± SD)	96.9±37.3	97.9±29.2
Serum creatinine- mg/dl (Mean ± SD)	0.95±0.31	0.99±0.44
Left Ventricular function after index event		
Normal (Ejection fraction >55%) - no. (%)	18 (29.5)	19 (30.2)
Mild impaired (Ejection fraction 45-54%) - no. (%)	16 (26.2)	17 (27.0)
Moderate impaired (Ejection fraction 36-44%) - no. (%)	10 (16.4)	18 (28.6)
Severely impaired (Ejection fraction<35%) - no. (%)	17 (27.9)	9 (14.3)
*There were no significant differences between groups		

Table-1: Baseline characteristics of the study population*

outcome were measured as major bleed at discharge and by 30 days, classified as type 3–5 according to the Bleeding Academic Research Consortium (BARC)¹⁶ definition. Secondary outcome seen were stent thrombosis rates, cardiac enzyme release, and any bleeding.

Data Collection: After the PCI, once patient was shifted out of the coronary intervention lab, data was collected. General consent taken at the time of admission was used to get the access of clinical, biochemical and radiological data required in the study. Blood sampling was done 12–18 h after the index procedure to assess creatine kinase (CK)-MB concentration in all patients. Also an echocardiography was performed post procedure as a part of routine protocol of the department.

Follow Up: Patients were contacted telephonically after 30 – 40 days of PCI. Contact number was taken at the time of enrollment. Data was collected as per Annexure II.

Sub group analysis: A sub group analysis was done. Assessment of the primary outcome was done according to the route of arterial vascular access, left ventricular function, age, diabetes and post procedure TIMI score.

Sample Size Calculation: Under the assumption that the incidence of major adverse ischemic events are around 7.5% in the setting of PPCI, with no increase in bleeding complications, the sample size worked out around 55 in each group with 95% confidence level, 80% power and 10% precision.

STATISTICAL ANALYSIS

The analysis included profiling of patients on different demographic and clinical as well as treatment outcome parameters. Descriptive analysis of quantitative parameters was expressed as means and standard deviation. Ordinal data was expressed as percentage. The analysis done was mainly univariate. T-test was used for the comparisons among groups. P-value < 0.05 was considered statistically significant. All analysis was done using SPSS. In view of no adverse event in heparin arm, risk ratio could not be calculated as done in most of other international studies. Hence P value was calculated by two proportion test and Z value was obtained.

RESULTS

Baseline characteristics: The baseline characteristics of patients in both the category 1 and category 2 are shown in Table 1.

Treatments and procedures: Treatments and procedures are summarized in Table-2.

Outcome at discharge: Outcomes seen at discharge were primary efficacy outcome and primary safety outcome (Table-3,4). Primary efficacy outcome was measured as the proportion of patients who had at least one major adverse cardiac event (MACE). Primary safety outcome was measured as the proportion of patients who had major

	Heparin (N=61)	Bivalirudin (N=63)
Aspirin use- no. (%)	61 (100.0)	63 (100.0)
P2Y12 inhibitor loading dose- no. (%)		
Prasugrel	7 (11.5)	5 (7.9)
Clopidogrel	22 (36.1)	20 (31.7)
Ticagrelor	32 (52.5)	38 (60.3)
Glycoprotein IIB/IIIA inhibitor- no. (%)	21 (34.4)	0 (0.0)
Arterial access site - no. (%)		
Femoral	56 (91.8)	63 (100.0)
Radial	5 (8.2)	0 (0.0)
Single vessel disease- no. (%)	44 (72.1)	44 (69.8)
Infarct related artery- no. (%)		
Left main	1(1.2)	2 (2.4)
Left anterior descending	39 (48.8)	43 (52.4)
Left circumflex	18 (22.5)	20 (24.4)
Right	18 (22.5)	16 (19.5)
Saphenous vein graft	0 (0.0)	1 (1.2)
Ramus Intermedius	4 (5.0)	0 (0.0)
Ballon angioplasty only - no. (%)	0 (0.0)	3 (3.6)
Implantation of stent- no. (%)		
1. Any type	61 (100.0)	60 (95.2)
2. Drug eluting	61 (100.0)	60 (95.2)
3. BVS	6 (9.8)	8 (12.7)
4. Bare metal	0 (0.0)	0 (0.0)
TIMI flow-- no. (%)		
Before PCI		
0 to 1	20 (32.8)	32 (50.8)
2	9 (14.8)	19 (30.2)
3	32 (52.2)	12 (19.0)
After PCI		
0 to 1	0 (0.0)	0 (0.0)
2	1 (1.6)	4 (6.3)
3	60 (98.4)	59 (93.7)
Activated clotting time- secs (Mean ± SD)		
5-15 minutes after bolus dose	331.7±70.8	382.2±85.4
At the end of procedure	312.3±59.3	363.7±81.2
Creatine kinase MB-U/L (Mean ± SD)		
Before procedure	82.5±106.8	64.2±90.1
After procedure	52.3±58.3	62.3±86.8
Medications at discharge- no. (%)		
Aspirin	61 (100.0)	61 (100.0)
Beta-blocker	45 (73.8)	55 (90.2)
ACE inhibitor	34 (55.7)	48 (78.7)
P2Y12 inhibitor	61 (100.0)	61 (100.0)
Statin	61 (100.0)	60 (98.4)

Table-2: Procedures and study medications

bleeding. MACE was observed in the two cases in the bivalirudin group while heparin group showed no MACE. Both MACE were attributed to mortalities. One death was due to cardiac cause and the other due to noncardiac etiology. No case of cerebrovascular accident, reinfarction or unplanned target lesion revascularization was observed in either group. Major bleeding was seen in only one patient who received bivalirudin. No statistically significant difference was observed between heparin and bivalirudin

	Heparin (N=61)	Bivalirudin (N=63)	Z - value	P - value
Total MACE- no. (%)	0 (0.0)	2 (3.2)	1.4	0.159
Death- no. (%)	0 (0.0)	2 (3.2)	1.4	0.159
Cardiac causes	0 (0.0)	1 (1.6)	1	0.321
Non cardiac causes	0 (0.0)	1 (1.6)	1	0.321
Cerebrovascular accident	0 (0.0)	0 (0.0)	-	-
Reinfarction	0 (0.0)	0 (0.0)	-	-
Unplanned target lesion revascularization	0 (0.0)	0 (0.0)	-	-

*MACE is a composite of all-cause mortality, cerebrovascular accident, reinfarction, or additional unplanned target lesion revascularization.

Table-3: Primary efficacy outcomes measures or Major Adverse Cardiovascular Event (MACE) at discharge*

	Heparin (N=61)	Bivalirudin (N=63)	Z - value	P - value
Any type of bleed; n (%)	2 (3.3)	3 (4.7)	0.4	0.691
BARC Type 1	2 (3.3)	2 (3.2)	0.001	0.975
BARC Type 2	0 (0.0)	0 (0.0)	-	-
BARC Type 3-5 (Major bleeding) or Primary safety outcome measures	0 (0.0)	1 (1.6)	1	0.321

Table-4: Bleeding outcome at discharge

	Heparin (N=61)	Bivalirudin (N=63)	Z - value	P - value
Total MACE- no. (%)	0 (0.0)	3 (4.7)	1.7	0.087
Death- no. (%)	0 (0.0)	2 (3.2)	1.4	0.159
Cardiac causes	0 (0.0)	1(1.6)	1	0.321
Non cardiac causes	0 (0.0)	1(1.6)	1	0.321
Cerebrovascular accident	0 (0.0)	0 (0.0)	-	-
Reinfarction	0 (0.0)	1 (1.6)	1	0.321
Unplanned target lesion revascularization	0 (0.0)	1 (1.6)	1	0.321

*MACE is a composite of all-cause mortality, cerebrovascular accident, reinfarction, or additional unplanned target lesion revascularization

Table-5: Primary efficacy outcomes measures or Major Adverse Cardiovascular Event (MACE) at 30 days*

	Heparin (N=61)	Bivalirudin (N=63)	Z - value	P - value
Any type of bleed; n (%)	6 (9.8)	6 (9.5)	0.1	0.955
BARC Type 1	6 (9.8)	5 (7.9)	0.4	0.709
BARC Type 2	0 (0.0)	0 (0.0)	-	-
BARC Type 3-5 Major bleeding) or Primary safety outcome measures	0 (0.0)	1(1.6)	1	0.321

Table-6: Bleeding outcome at 30 days

regarding efficacy and safety outcome.

Outcome at 30 days: Outcomes seen at 30 days were MACE and bleeding outcomes (including events prior to discharge) (Table 5, 6). There was one additional MACE in form of stent thrombosis and myocardial infarction in bivalirudin group. There was no statistically significant difference for MACE and bleeding outcome in two groups even after 30 days.

Secondary outcomes: Secondary outcomes seen were stent thrombosis rates, reduction in cardiac enzyme and any bleed. One case of sub acute definitive stent thrombosis was noted in bivalirudin group, whereas no such event was seen in heparin group, though this difference was not statistically significant. (P=0.321) CPK-MB pre and post procedure was available in 34 patients in heparin group and 39 patients in

bivalirudin group. Mean change for CPK-MB was +11.7 in heparin group and -21.3 in bivalirudin group. But because of very high standard deviation, this difference was not statistically significant. Rate of bleeding events did not differ between groups.

Subgroup analysis: Assessment of the MACE was done according to the age, left ventricular ejection fraction, TIMI flow, route of arterial vascular access and history of diabetes. Mean age was higher in MACE group. (62.7% vs. 58.3% and 57.5%). All the 3 MACE happened in left ventricular dysfunction individuals each in mild, moderate and severe dysfunction. Mean increase in TIMI flow was higher in MACE group (2% vs. 0.92% and 1.5%). Two out of three were diabetic i.e. 66.6% comparing with 39.3% and 46.7% of no MACE arm of heparin and bivalirudin respectively. No

radial access was used in any of the bivalirudin group. All the findings were statistically non-significant.

DISCUSSION

In the present observational study it was shown that there was no significant difference in the primary efficacy outcome between heparin with provisional glycoprotein IIb/IIIa inhibitor and the bivalirudin group with provisional glycoprotein IIb/IIIa inhibitor. Primary efficacy outcome in our study was measured as the proportion of patients who had at least one major adverse cardiac event (MACE). Patients in the bivalirudin group showed a MACE incidence of 3.2% (2 out of 63) at discharge, and 4.7% (3 out of 63) at 30 days. Heparin group showed no MACE. Most of the earlier large trials have shown that bivalirudin is as good as heparin with respect to efficacy outcomes except, HEAT-PPCI which showed significantly higher rates of MACE in bivalirudin group.^{3,5,6,10,14,15} In our study although MACE was more with bivalirudin, but it was not statistically significant. MACE at 30 days in our study in bivalirudin group is comparable to MACE in most of the trials.^{3,5,6,10,14,15} HORIZONS-AMI done in 2008 included patients with STEMI undergoing primary PCI⁵ which reported 5.4% MACE in bivalirudin group. EUROMAX (2013) also reported MACE incidence of 5% in bivalirudin group.⁶ MACE in ISAR- REACT 3 was calculated at 1 year which came out to be 17.1% and was similar to heparin group.⁸ When compared with the other Indian studies, Seth et al (2008) showed only 0.68% MACE in moderate to high risk patients going for PCI who received bivalirudin.¹² There was no comparison arm. Deshpande et al (2012) reported no adverse outcome in both the arms at 30 days.¹³

Two mortalities occurred in our study, one from cardiac and second from non-cardiac etiology. Both patients died during same hospitalization. Subsequently no additional mortality was seen at 30 days. Death in one patient was attributed to bilateral pneumonia and septic shock, with underlying COPD. The second patient developed ventricular arrhythmias after PCI and subsequently died off cardiogenic shock. He also had severe left ventricular dysfunction pre PCI. Though two patients died in the bivalirudin group, but it was not statistically significant when compared with heparin. No patient suffered from cerebrovascular accident in either group. Reinfarction and subsequent revascularization was seen in one patient (1.6%) at 30 days follow up who received bivalirudin.

Our study shows no significant difference in death rate in both bivalirudin and heparin arm, which is in concordance with various trials except HORIZON-AMI which showed rates of death from cardiac causes and from all causes were significantly lower with bivalirudin alone (3.1% vs. 2.1% $p=0.047$).^{3,5,6,8,10,14,15} Mortality rate (3.2%) of bivalirudin arm of our study is compared with other studies (1 to 2.9%) except HEAT-PPCI, which showed 5.1% mortality in patients who received bivalirudin.¹⁰ No mortality was observed in our study amongst patients who received heparin. This again can be attributed to selection bias and small number of cases

being observed.

Safety outcome i.e. major bleed favors bivalirudin in most of the studies.^{3,5,6,8,14,15} But our study showed there was no significant difference in the incidence of major bleeding in both groups (1.6% in bivalirudin v/s 0% in heparin, $p=0.32$). Similar finding was also observed in one major trial HEAT-PPCI which showed similar incidence of major bleeds in both groups (3.5% in bivalirudin v/s 3.1% in heparin, $p=0.59$).¹⁰ Overall incidence of major bleed has gone down significantly in recent years both with heparin and bivalirudin. In 2007 and 2008 it was as high as 7% - 8.3% compared to last year results as low as 1.5% - 2.5%. Bleeding rates are further low with bivalirudin. Incidence of major bleed in bivalirudin arm in our study was 1.6%. It is in concordance with the various trials where major bleeding incidence has been observed from 0.5% to 4%. Variable rates of major bleeding have been observed in the heparin group. Recent trials BRIGHT (2015) and MATRIX (2015) have shown major bleeding rate of 1.5% and 2.5% respectively.^{14,15} But major bleeding rate was more in the heparin group in the older trials. ACUITY (2007) reported major bleeding rate of 7% and HORIZONS-AMI (2008) reported major bleeding rate of 8.3% in the heparin group.^{3,5} In our study, no patient in the heparin group had major bleeding. Again selection bias and small number of cases being observed can be the explanation. We could not find any Indian data on incidence of major bleed with bivalirudin. Our findings revealed, heparin and bivalirudin are similar in both efficacy and safety parameters. Though we had three MACE and one major bleed in bivalirudin arm comparing with no adverse event in heparin, this difference is statistically not significant. This difference further reduces if we do not include one death, which was of non cardiac cause. If we see event rates in different trials conducted in the era of DAPT and drug eluting stents, events rates of our study in bivalirudin arm are comparable with events rates in bivalirudin arm of other international studies.^{3,5,6,7,8,10,12,13,14,15,23,24}

Secondary outcomes studied were stent thrombosis rate, rate of any bleeding and cardiac enzyme release. In all major studies stent thrombosis rate is 0.5% to 1% in heparin group where as 0.6% to 3.4% in bivalirudin group.^{3,5,6,8,10,14,15} Initially it was considered as equal in both the groups, but EUROMAX in 2013 showed reduced bleeding rates at the expense of increased acute stent thrombosis in bivalirudin arm (1.6% v/s 0.5% $p=0.02$).⁶ Later similar findings came out from HEAT PPCI (2014) and MATRIX (2015) which also showed significantly higher rates of stent thrombosis with bivalirudin (3.4% v/s 0.9% $p=0.001$ and 1.0% v/s 0.6%, $p=0.48$).^{10,15} Increased rate of stent thrombosis in bivalirudin was also observed in HORIZONS-AMI, though this difference was not statistically significant (2.5% vs 1.9%, $p=0.3$).⁵ In our study also, increased rate of stent thrombosis was observed with the bivalirudin though this difference was not statistically significant (1.6% vs. 0%, $p=0.32$). In contrast, one large randomized, multicentre trial, BRIGHT trial showed decreased rate of stent thrombosis in bivalirudin arm though this difference was not statistically significant

(0.6% in bivalirudin vs. 0.9% in heparin.¹⁴ Present study showed one case of sub-acute, definitive stent thrombosis (1.6%) in bivalirudin group, where as no such event was noted in heparin arm. Patient came within week of discharge, with acute anterior wall MI. Coronary angiography revealed 100% in stent thrombosis of LAD stent.

Any bleed: All the earlier RCT's showed rate of any type of bleed, between 7.5% to 13.6% in heparin group and 4.1% to 12.5% in bivalirudin group. Most of the trials showed that rate of any type of bleeding were significantly higher with heparin as compared to bivalirudin.^{3,5,6,8,10,14,15} But HEAT-PPCI showed no significant differences in rate of any type of bleeding in heparin arm (13.6% v/s 11.0% p=0.001). Similarly, our study showed near equal rates of all type bleed in both arms 9.8% v/s 9.5% in heparin and bivalirudin group respectively.

CKMB reduction: Mean pre-procedural CK-MB levels were 82.5±106.8 and 64.2±90.1 in heparin and bivalirudin group respectively. Mean post-procedural CK-MB levels were 52.3±58.3 and 62.3±86.8 in heparin and bivalirudin group respectively. Older studies has shown release of CK-MB post PCI to occurs in 20% of patients, including elevations of up to 3 times the upper normal limit in at least 8% of patients. So even this small elevation in heparin arm is not out of the limit of what is documented in older studies.^{17,18} The incidence of Net Adverse Cardiac Events (NACE), was more in the bivalirudin group with provisional GP IIB/IIIa inhibitor as compared to heparin with provisional GP IIB/IIIa inhibitor (p=0.045). NACE was considered as composite of MACE and major bleeding. Incidence of NACE was 4.8% at discharge and 6.4% at 30 days follow up in the bivalirudin recipients. No patient in the heparin group had NACE, though incidence of NACE was not statistically significant in two groups at time of discharge. It was significantly more in the bivalirudin group when followed at 30 days. Probable explanation of higher rates of NACE in this arm is the same that we discussed in the section of MACE, i.e. high risk patients were significantly higher in bivalirudin group, based on pre TIMI scores. If we do not consider non cardiac death, then this becomes statistically insignificant. Overall if we compare the NACE rates of our study with older studies, our rate is lowest among all the studies comparing bivalirudin and heparin. NACE rates are between 10.6% - 13.2% in heparin group, where as 7.8% to 15% in bivalirudin group. The only statistical significant difference in NACE was shown in HORIZONE-AMI, which said bivalirudin is superior to heparin (9.2% v/s 12%, p=0.005).^{3,5,6,8,10,14,15} Higher rates of repeat hospitalization in bivalirudin arm. 4 out of 63 (6.4%) patients got readmitted who had received pre-procedure bivalirudin. 3 (4.7%) from cardiac cause one from non cardiac cause. One had sub-acute definitive stent thrombosis, as discussed earlier in MACE section, 2 had severe left ventricular dysfunction and got readmitted with left ventricular failure and pulmonary edema and one developed contrast induced nephropathy and got admitted with acute on chronic kidney injury. All four patients later

got discharged without any further adverse events.

Overall repeat hospitalization rates from any cause in our study are lower than other published data which studied repeat hospitalization post PCI. Repeat hospitalization from cardiac cause is comparable with older studies. Older studies have shown repeat hospitalization from any cause post PCI, between 12.5% - 14%. Cardiac cause of re-admission is shown to be 4.6% - 6.5%.¹⁹⁻²²

None of the bivalirudin recipient received GP IIB/IIIa inhibitor. Also higher number of patients (statistically significant difference) with 0-1 TIMI flow pre-procedure received bivalirudin. May be the clinicians do not prefer using GP IIB/IIIa inhibitor concomitant with bivalirudin and prefer using bivalirudin in high risk subset population, as most of the studies had shown non-inferiority with added advantage of lesser bleeding with bivalirudin.^{3,5,6,8,10,14,15} In present study, there were four events, three MACE and major bleed and this happened in three patients as one of the patients which died of non-cardiac cause had major bleed post-procedure.

Bioresorbable vascular scaffold in ACS patients: 14 ACS patients received bioresorbable Vascular Scaffold, 6 from heparin group and 8 from bivalirudin group. None had any MACE or any major bleed.

Overall event rate is very low compared to other international RCT's. If we combine event rates from both groups and calculate MACE and major bleed in 123 tandem ACS patients, it comes out to be 2.4% and 0.8% respectively, which if we compare with other international RCT's, it is significantly low.^{3,5,6,8,10,14,15} Possible reasons for these findings can be: 1) Liberal use of intravascular imaging modalities e.g. FFR, IVUS and OCT, 2) Higher stent implantation pressures and 3) 4-6 hours post PCI infusion of bivalirudin in bivalirudin arm. Though this was not proven to be beneficial in MATRIX trial. But, this is the only one trial studied and may be in future trials shows favorable outcome with prolonged infusion. At least theoretically prolonged infusion post PCI seems logical, especially in cases with high thrombus load.

CONCLUSION

In conclusion, our study we could not find any statistically significant difference in 30 days efficacy and safety outcome in two groups, one receiving bivalirudin with provisional planned glycoprotein IIB/IIIa blockade and other heparin with provisional planned glycoprotein IIB/IIIa blockade. Though there were 3 MACE and 1 major bleed in bivalirudin arm comparing with no such event in heparin arm but this difference was not statistically significant. More trials comparing the two drugs in different clinical situations are required to give any conclusive evidence.

Abbreviations:

ACS - Acute coronary syndrome

GPI - Glycosylphosphatidylinositol

TIMI -Thrombolysis in myocardial infarction

MACE – Major adverse cardiac events

UA – Unstable angina
 NSTEMI – non ST elevation myocardial infarction
 STEMI – ST elevation myocardial infarction
 MI – Myocardial infarction
 AHA – American heart association
 PCI – Percutaneous coronary intervention
 BARC – Bleeding academic research consortium
 COPD – Chronic obstructive pulmonary disease
 CKMB – Creatinine kinase muscle/brain
 NACE – Net adverse cardiac events
 DAPT – Dual antiplatelet therapy

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