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Comparison of anti-thrombotic strategies using Bivalirudin, Heparin plus Eptifibatide, and Unfractionated Heparin Monotherapy for acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI): A single-center observational study

A.B.M. GOLAM MOSTOFA, TANJIMA PARVIN, MRM MANDAL, PALLOB KUMAR BISWAS, GOUTOM CHANDRA BHOWMIK, FYSAL FARUQ, SYED ALI AHSAN

Department of Cardiology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka, Bangladesh

Address of Correspondence: Dr. A. B. M. Golam Mostofa, Resident , UCC, BSMMU , Dhaka. Bangladesh; E-mail: drmostofabd@gmail.com

Abstract:

Objective: To determine and compare the incidence of in-hospital and 30-day hemorrhagic complication and major adverse cardiac events (MACEs) as evidence of safety and efficacy using three different anti- thrombotic strategies using Bivalirudin, Heparin plus Eptifibatide (GPI: GP IIb/IIIa inhibitor), and Unfractionated Heparin (UFH) monotherapy in acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI) in a tertiary care cardiac hospital.

Background: UFH or Heparin plus Eptifibatide or Bivalirudin is the most commonly used antithrombotic regimen to improve peri and post-PCI clinical outcomes in a patient undergoing PCI for ACS. Among them, the most effective and optimal antithrombotic regimen for preventing ischemic complications while limiting bleeding risk in ACS patients undergoing PCI is still far from being clear.

Methods: 324 ACS patients (age >18 years and ≤75 years) who underwent PCI from May 2018 to May 2019 at UCC, BSMMU, Dhaka were consecutively enrolled in the study and were divided into three groups according to antithrombotic. The choice of Anti-thrombotic strategy was at the discretion of the operator(s) and the patient's affordability. Group-A: 107 patients received Bivalirudin as intravenous (I/V) bolus of 0.75 mg/kg, followed by an infusion of 1.75 mg/kg/hr up to 4 hours. Group-B: 111 patients received UFH as an I/V bolus of 70-100 U/kg (targeted ACT: 250-300 s). Group-C: 106 patients were administered UFH plus Eptifibatide as per the standard hospital guidelines. Dual antiplatelet (DAPT) loading as Aspirin 300 mg plus P2Y12 inhibitors (Clopidogrel 600 mg or Prasugrel

60 mg or Ticagrelor 180 mg) was given in all patients before the procedure. The maintenance dose of DAPT was continued for at least one month and patients were followed telephonically up to 30 days. The outcome measures were in-hospital and 30-day hemorrhagic complication and MACEs [death, MI, stroke, stent thrombosis and target-vessel revascularization (TVR)]

Results: In-hospital outcome: Patients treated with Bivalirudin as compared with UFH had a significantly lower incidence of QMI lesions (0% vs.6%; p=0.038) and major bleeding (0% vs. 7%; p=0.021). The bleeding rate was also significantly lower in Bivalirudin arm as compared with Heparin plus GPI arm (0% vs. 6%; p=0.038). However, the incidence of cardiac death, stent thrombosis, TVR were no differences among the three groups. 30-day outcome: There was only one NQMI in the bivalirudin group as opposed to 8% in the heparin group (p=0.041). No other adverse effects were found significantly different among the study groups.

Conclusion: In this perspective, observational study of ACS patients undergoing PCI in a single-center showed that Bivalirudin monotherapy is safer than other contemporary antithrombotic strategies. In terms of efficacy, Bivalirudin is non inferior to Heparin plus Eptifibatde but superior to UFH monotherapy.

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Introduction:

Acute coronary syndromes (ACS) represent the principal form of clinical presentation of coronary artery disease (CAD).[1] CAD is a growing epidemic in South Asia and is the leading cause of mortality in the Indian subcontinent,[2] as well as Bangladesh.[3]

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PCI in conjunction with antithrombotic drugs is the most effective remedy for ACS.[4] Anticoagulation with UFH or Heparin plus GPI (Eptifibatide) or Bivalirudin, in combination with DAPT (Aspirin plus P2Y12 inhibitors), is the most commonly used antithrombotic regimen to improve peri and post -PCI clinical outcomes in a patient undergoing PCI for ACS.[4]

Identification of most appropriate adjunctive antithrombotic therapy before, during, and after PCI has been the target of extensive research for the past three decades.[5]

UFH is traditionally regarded as the standard anticoagulant strategy during PCI though it has an intrinsic limitation. UFH cannot inhibit thrombin without antithrombin-III or heparin cofactor-II. UFH binds to several plasma proteins, endothelial cells, vWF, and macrophages, which reduces its anticoagulant activity, leads to heparin resistance. Relatively rapid clearance of UFH produces a heparin rebound effect i.e. increased thrombin activity within a few hours after its cessation. So, UFH may cause heparin- induced thrombocytopenia (HIT), unpredictable pharmacokinetics, a highly variable dose-response relation, resulting in a narrow therapeutic window.[6-10] To overcome these limitations GPI invariably uses with heparin during PCI which is costly and increases the risk of bleeding.[11] Eptifibatide is a highly selective GPI and should be considered for a bail-out situation during PCI in both STEMI[12] and NSTE- ACS.[13]

Bivalirudin is a 20 amino acid polypeptide and is a reversible I/V direct thrombin inhibitor. It inhibits both circulating and clot bound thrombin as well as thrombin mediated platelet activation. It has linear pharmacokinetics and short half-life (~25 min) and lab monitoring of efficacy are not required.[14] Randomized clinical trials and various meta-analyses have shown that bivalirudin significantly reduces bleeding-related complications without compromising efficacy in ACS patients undergoing PCI.[4,15-20] Based on this evidence, Bivalirudin (0.75 mg/kg I .V. bolus, followed by 1.75 mg/kg/h for up to 4 h) is recommended as an alternative to UFH plus GPI during PCI in both STEMI[12] and NSTE-ACS.[13] However, previous studies that have compared UFH, heparin plus GPI, and bivalirudin monotherapy yielded contradictory results concerning ischemic, bleeding or combined outcomes.[21,22] The most effective and optimal antithrombotic regimen for preventing ischemic complications while limiting bleeding risk in ACS patients undergoing PCI is still far from being clear.

In the current study, we tried to determine and compare the incidence of in-hospital and 30-day hemorrhagic complications and MACEs as evidence of safety and effectiveness using three different anti- thrombotic strategies using Bivalirudin, Heparin plus Eptifibatide, and UFH monotherapy in ACS patients undergoing PCI in a tertiary care cardiac hospital.

Method:

Study population: In this perspective, observational study, 324 ACS patients (age >18 years and ≤75 years) who underwent PCI from May 2018 to, April 2019 at UCC, BSMMU, Dhaka were consecutively enrolled after exclusion of following criteria: patients with the chronic coronary syndrome, prior MI, prior revascularization, mechanical complication, prior thrombolytic within 8 hours, current use of warfarin, history of bleeding diathesis or known coagulopathy (including HIT), history of intracerebral mass, aneurysm, AVM, stroke within 6 months or any permanent neurologic deficit; GI or GU bleed within 2 months, or major surgery within 6 weeks; recent or known platelet count <100,000 cells/mm3 or hemoglobin <10g/dL, Cr Cl <30 ml/min. The study was approved by the institutional ethical committee and all patients gave written informed consent.

Study protocol

DAPT loading as Aspirin 300 mg plus P2Y12 inhibitors (Clopidogrel 600 mg or Prasugrel 60 mg or Ticagrelor 180 mg) was given in all patients at least 2 hours before PCI. The transfemoral approach for coronary angiography was undertaken by using a modified Seldinger technique with a 7F introducer sheath. After the decision had been made to perform a coronary intervention, the choice of Anti-thrombotic strategy was at the discretion of the operator(s) and the patient's affordability. According to antithrombotic, patients were divided into three groups. Group-A: 107 patients received Bivalirudin as I/V bolus of 0.75 mg/kg, followed by an infusion of 1.75 mg/kg/h up to 4 hours. Group-B: 111 patients received UFH as an I/V bolus of 70-100 U/kg (targeted activated clotting time, ACT: 250-300 s). Group- C: 106 patients received UFH plus Eptifibatide as per the standard hospital guideline. Coronary stenting with drug-eluting stent (DES) was performed according to the discretion of the operator and caregiver's choice. Less than 30% residual stenosis after the procedure was counted as successful PCI. Sheaths were removed and manual compression was applied as soon as the ACT fell below 150 s. The patients were mobilized after 6 h of sheath removal and were typically

discharged from the hospital 24-48 h after the procedure. The maintenance dose of DAPT was continued for at least one month after PCI. All patients were followed up over telephone or OPD consultation for 30 days for hemorrhagic complication and MACEs (death, Recurrent MI, Urgent TVR for ischemia, and stroke).

Study endpoints

The outcome measures were in-hospital and 30-day hemorrhagic complications and MACEs. The definition of major bleeding was based on (REPLACE-2) trial and included intracranial, intraocular, or retroperitoneal hemorrhage; clinically overt blood loss resulting in a decrease in hemoglobin of more than 3 g/dl, any decrease in hemoglobin of more than 4 g/dl; or transfusion of 2 or more units of packed red cells or whole blood.[4] Recurrent MI was defined in the presence of both ischemic pain and a new >50% increase in Troponin I level. The MI definitions were adapted from the Joint European Society of Cardiology/American College of Cardiology Committee statement on the universal definition of MI.[23] Death from cardiac causes was defined as death due to acute MI, cardiac perforation or pericardial tamponade, arrhythmia or conduction abnormality, stroke, procedural complications, or any death for which a cardiac cause could not be ruled out. Stent thrombosis was defined according to the Academic Research Consortium classification.[24]

Statistical analysis

Statistical analyses were conducted using the Statistical Package for Social Science (SPSS) version 23.0 windows software. Parametric data were expressed in mean ± SD and analyzed by Student's t-test. Categorical data were expressed as frequencies and percentages and analyzed by Chi-Square test. p-value < 0.05 is considered significant.

Results:

The present study, intended to compare the safety and effectiveness of three different antithrombotic regimens using bivalirudin or UFH or Heparin plus Eptifibatide in PCI, included a total of 324 ACS patients, who underwent PCI were consecutively enrolled and divided into three groups according to antithrombotic. 107 patients were in Bivalirudin arm, 111 patients received UFH and 106 patients were administered UFH plus Eptifibatide. Among them, 7 patients in bivalirudin, 11 patients in UFH and 6 patients in Eptifibatide arm had lost to follow up. So, finally, a total of 100 patients were in each group. The outcome measures were in-hospital and 30-day morbidity (complications or adverse events) and mortality. The findings of the study obtained from data analyses are documented below:

Table-I

Characteristics of the Patients at Baseline

Characteristic	Bivalirudin (n=100)	Heparin (n=100)	P_1-value ¥	Heparin+ Eptifibatide (n=100)	P2-valueI§
Age (years)	53.49±9.9	52.99±8.9	a0.710ns	55.61±11.8	a0.170 ns
Male sex, n (%)	90 (90.0)	81 (81.0)	b0.070ns	80 (80.0)	b0.075ns
BMI (kg/m2)	24.21±2.7	23.82±2.8	a0.317ns	25.02±3.6	a0.073ns
Diabetes mellitus , n (%)	73(73.0)	69(69.0)	b0.640ns	67(67.0)	b0.440ns
Hypertension, n (%)	69 (69.0)	64 (64.0)	b0.453ns	71(71.0)	b0.877ns
Dyslipidemia, n (%)	65 (65.0)	58 (58.0)	b0.069ns	59(59.0)	b0.467ns
Current smoker, n (%)	48 (48.0)	46 (46.0)	b0.776ns	52(52.0)	b0.672ns
Renal insufficiency,* n (%)	4(4.0)	3 (3.0)	b0.700ns	5(5.0)	b1.00ns
Family history of CAD, n (%)	12 (12.0)	19 (19.0)	b 0.171ns	16(16.0)	b 0.540ns
Previous Myocardial infarction, n (%)	29 (29.0)	23 (23.0)	b0.420ns	20(20.0)	b0.189ns
Previous coronary intervention, n(%)	3 (3.0)	1 (1.0)	b0.613ns	4(4.0)	b1.00ns
Previous stroke, n (%)	2(2.0)	1 (1.0)	b0.561ns	3(3.0)	b1.00ns
Peripheral vascular disease, n (%)	1 (1.0)	1 (1.0)	b0.477ns	2(2.0)	b1.00ns

¥P1 = comparison between bivalirudin vs. heparin . I§P2=comparison between Bivalirudin vs.(heparin + Eptifibatide)
* Calculated Creatinine clearance < 60 ml/min using the Cockcroft- Gault equation. ns=not significant.
a=P value reached from unpaired t-test. b=P value reached from Chi-square test. CAD=coronary artery diseases

Table-II

Clinical presentation and Medications at Baseline.

Characteristic	Bivalirudin (n=100)	Heparin (n=100)	P_1-value ¥	Heparin+ Eptifibatide (n=100)	P_2-value
Clinical presentation:					
ST-segment elevation myocardial infarction, STEMI, n(%)	69 (69.0)	63 (63.0)	[b]0.370ns	71(71.0)	b0.877ns
Non-STEMI, n (%)	27 (27.0)	26 (26.0)	[b]0.872ns	22(22.0)	b0.510ns
Unstable angina, n (%)	4 (4.0)	11 (11.0)	[b]0.060ns	7(7.0)	b0.536ns
Systolic arterial pressure (mmHg)	126.55±13.5	125.75±14.6	[a]0.688ns	127.7±11.2	a0.512ns
Heart rate (beats/min)	67.01±5.8	65.32±7.2	[a]0.070ns	66.22±5.3	a0.315ns
LVEF e”40 %, n (%)	88 (88.0)	81 (81.0)	[b]0.171ns	85(85.0)	b0.679ns
CKMB /Troponin I Elevated n (%)	96 (96.0)	89 (89.0)	[b]0.060ns	93(93.0)	b0.536ns
HbA1c (%)	9.79±1.9	9.53±1.9	[a]0.349ns	9.64±1.3	a0.515ns
Medication administered before catheterizationprocedure-no.(%):					
Aspirin + Ticagrelor, n (%)	89 (89.0)	90 (90.0)	[b]1.000ns	91(91.0)	b0.814ns
Aspirin + Clopidogrel , n (%)	1 (1.0)	6 (6.0)	[b]0.123ns	2(2.0)	b1.00ns
Aspirin + Prasugrel, n (%)	10 (10.0)	4 (4.0)	[b]0.096ns	7(7.0)	b0.612ns

¥P1 = comparison between bivalirudin vs. heparin. I§P2= comparison between Bivalirudin vs. heparin+ Eptifibatide, a=P value from unpaired t-test. b=P value from Chi-square test . LVEF= Left ventricular ejection fraction

Table III

Angiographic and procedural characteristics

Characteristic	Bivalirudin (n=100)	Heparin (n=100)	P_1-value ¥	Heparin+ Eptifibatide (n=100)	P_2-value
Femoral approach, n (%)	100(100.0)	100(100.0)	-	100(100.0)	-
Severity of disease:					
Single vessel disease, n (%)	42 (42.0)	47 (47.0)	b0.569ns	51(51.0)	b0.256ns
Double vessel disease, n (%)	45 (45.0)	33 (33.0)	b0.082ns	40(40.0)	b0.568ns
Triple vessel disease, n (%)	13 (13.0)	20(20.0)	b0.253ns	9(9.0)	b0.498ns
Lesion characteristics:					
Type-A, n (%)	53 (53.0)	47 (47.0)	b0.396ns	55(55.0)	b0.887ns
Type-B, n (%)	41 (41.0)	46 (46.0)	b0.476ns	40(40.0)	b1.00ns
Type-C, n (%)	6 (6.0)	7 (7.0)	b0.774ns	5(5.0)	b1.00ns
Procedural Characteristics:					
Number of treated lesions per patient	1.78±0.76	1.74±.0.76	a0.710ns	1.72±0.74	a0.572ns
Number of stents per patient	1.61±0.7	1.67±0.8	a0.592ns	1.60±0.73	a0.921ns
Intervention on LAD , n (%)	64 (64.0)	66 (66.0)	b0.766ns	68(68.0)	b0.655ns
Intervention on RCA , n (%)	42 (42.0)	44 (44.0)	b0.775ns	46(46.0)	b0.669ns
Intervention on LCX , n (%)	31 (31.0)	37 (37.0)	b0.370ns	33(33.0)	b0.879ns
Use of drug eluting stent, n (%)	100(100.0)	100(100.0)	-		
Stent length (mm), mean	26.42±5.2	25.55±6.3	a0.292ns	26.64±9.2	a0.835ns
Stent diameter (mm),mean	2.94±0.3	2.90±0.3	a0.274ns	2.96±0.38	a0.679ns
Procedural complication:					
Major dissection, n (%)	1 (1.0)	2 (2.0)	b0.750ns	1(1.0)	-
Slow/No reflow, n (%)	6 (6.0)	7 (7.0)	b0.774ns	5(5.0)	b1.00ns

¥P1 = comparison between bivalirudin vs. heparin. I§ P2= comparison between Bivalirudin vs.(heparin+ Eptifibatide) ns=not significant. a=P value reached from unpaired t-test. b=P value reached from the Chi-square test.

Table-IV
In-hospital clinical outcome

Outcome	Bivalirudin (n=100)	Heparin (n=100)	P_1-value ¥	Heparin+ Eptifibatide (n=100)	P_2-value
Efficacy endpoints (MACEs)					
Cardiac death, n (%)	1 (1.0)	4 (4.0)	0.366ns	2(2.0)	1.00ns
Reinfarction: Q-wave MI, n (%)	0 (0.0)	6 (6.0)	0.038s	2(2.0)	0.477ns
Reinfarction: Non Q-wave MI, n (%)	1 (1.0)	4 (4.0)	0.366ns	3(3.0)	0.614ns
Stent thrombosis, n (%)	0(0.0)	2(2.0)	0.477ns	1(1.0)	1.00ns
Target vessel revascularization, n (%)	0(0.0)	2(2.0)	0.477ns	1(1.0)	1.00ns
Safety end points (hemorrhagic events)					
Major bleeding, n (%)	0 (0.0)	7 (7.0)	0.021s	6(6.0)	0.038s
Minor bleeding, n (%)	2(2.0)	4(4.0)	0.678s	3(3.0)	1.00ns
Vascular access site complication, n(%)	2(2.0)	3(3.0)	1.00ns	2(2.0)	0.613ns

¥P1 = comparison between bivalirudin vs. heparin. I§ P2= comparison between Bivalirudin vs. (heparin+ Eptifibatide)
ns=not significant. s= significant . P value reached from Chi-square test . MACEs= major adverse cardiac events.

Table-V
Clinical outcome of up to 30 days

Outcome	Bivalirudin (n=100)	Heparin (n=100)	P_1-value ¥	Heparin+ Eptifibatide (n=100)	P_2-value
Efficacy endpoints (MACEs)					
Cardiac death, n (%)	0 (0.0)	1 (1.0)	1.00ns	1(1.0)	1.00ns
Reinfarction: Q-wave MI, n (%)	1 (1.0)	2(2.0)	1.00ns	2(2.0)	1.00ns
Reinfarction: Non Q-wave MI, n (%)	1 (1.0)	8 (8.0)	0.041s	3(3.0)	0.614ns
Stent thrombosis, n (%)	0(0.0)	1(1.0)	1.00ns	1(1.0)	1.00ns
Target vessel revascularization, n (%)	0(0.0)	1(1.0)	1.00ns	1(1.0)	1.00ns
Stroke	0(0.0)	0(0.0)	—	1(1.0)	1.00ns
Safety end points (hemorrhagic events)					
Minor bleeding, n (%)	0(0.0)	0(0.0)	—	1(1.0)	1.00ns

¥P1 = comparison between bivalirudin vs. heparin. I§ P2= comparison between Bivalirudin vs. (heparin+ Eptifibatide)
ns=not significant. s= significant . P value reached from Chi-square test . MACEs= major adverse cardiac events.Patients and procedure:

The baseline demographic, clinical and procedural characteristics were well balanced between treatment groups.

The mean age in bivalirudin, UFH, and Heparin plus Eptifibatide arm were 53.49± 9.9 years, 52.99 ± 8.9 years, and 55.61± 11.8 years respectively. In all the three treatment groups, the mean age was statistically similar (Bivalirudin and Heparin; p=0.71, Bivalirudin, and Heparin plus GPI; p= 0.17, Heparin plus GPI and Heparin; p=0.07). A male predominance was observed in each group. DM was most common in Bivalirudin arm (73%) and hypertension was most common in Heparin plus Eptifibatide arm (71%). However, the distribution of risk factors like DM, hypertension, dyslipidemia, smoking were almost identical among the study group (p>0.05) (Table I).

The majority of the patients in each group present with STEMI and received DAPT in the form of Aspirin + Ticagrelor. Distribution of blood pressure, Heart rate, LVEF, HbA1c were almost identical in all the three study groups (P>0.05). Uncontrolled DM was observed in each group. (Table II)

In terms of lesion characteristics, the groups were almost homogeneous with Type-A lesion being higher in either group. LAD followed by RCA PCI was common in each group. Distribution of the number of treated lesions per patient, number of stent per patient, stent length and width were similar among the study group (p>0.05) (Table III).

Clinical outcomes (in-hospital)

In this study, the patients of the Bivalirudin group, as compared to the UFH group, had a significantly lower

incidence of Q-wave MI (0% vs.6 %; p=0.03) and major bleeding (0% vs. 7%; p=0.007). The incidence of major bleeding was also significantly lower in the Bivalirudin group, as compared to the Heparin plus Eptifibatide group (0% vs.6 %; p=0.03).

Cardiac death rate was less in Bivalirudin arm (1%) than UFH (4%) and (Heparin + Eptifibatide) arm (2%). Stent thrombosis was not reported in the Bivalirudin group but was seen in two patients of the UFH group and one patient of (Heparin + Eptifibatide) group. None of the patients underwent target lesion revascularization (TLR) and TVR within 24-48 hours of PCI other than two early definite stent thrombosis reported in UFH and one in (Heparin + Eptifibatide) arm. No Unplanned Revascularization for ischemia and stroke was observed in any group. However, the incidence of cardiac death, non-Q-wave MI, stent thrombosis, TLR & TVR, minor bleeding, and vascular access site complications were no different among the study groups (p>0.05) (Table IV)

Clinical outcomes (at 30 days)

There was only one QMI in the bivalirudin group as opposed to 8% in the UFH group in 30 days following stenting (p=0.04). Stent thrombosis was not reported in the Bivalirudin group but was seen in one patient of the UFH group and one patient of Heparin plus Eptifibatide group. None of the patients underwent target lesion revascularization (TLR) and TVR within 30-days of PCI other than one early definite stent thrombosis reported in UFH and one in (Heparin + Eptifibatide) arm. No other adverse effects were found significantly different among the study group in 30 days of PCI (Table V).[4]

Discussion:

In this perspective, observational study involving ACS patients who underwent PCI, treatment with Bivalirudin as compared to treatment with UFH, improved event-free survival up to 30 days, owing to a significant reduction in major bleeding and reinfarction (QMI and NQMI). The major bleeding rate was also significantly lower in the Bivalirudin group as compared to the Heparin + Eptifibatide group. The cardiac death rate was less in bivalirudin arm as compared to both UFH arm and Heparin + Eptifibatide arm. There was no incidence of stent thrombosis and UTVR at all in the bivalirudin group as opposed to 3% in the UHF group & 2% in the Heparin + Eptifibatide group up to 30 days of PCI.

In terms of the safety endpoint (bleeding risk) our study findings are consistent with literature.[4, 6,15-20] In an Indian study, Kaul et al. found that major bleeding was 1.59% in Bivalirudin, 5.97% in UFH arm and 3.49%in Heparin + GPI arm (p<0.005)20. In a meta-analysis, Zhang et al. have reported that bivalirudin decreases the risk of major bleeding more significantly than heparin (174 patients in bivalirudin vs. 297 patients in UFH experienced major bleeding: RR 0.63; 95% CI 0.52-0.75; P<0.00001)15. Nairooz et al. concluded that bivalirudin reduces major bleeding risk significantly in ACS patients following PCI (OR 0.68; 95% CI 0.52-0.89; P=0.005)19. Feit et al. have reported that major bleeding was 3.7% in bivalirudin arm and 7.1% in Heparin+ GPI arm (p<0.001) 25. Though, these results are contrary to the results of HEAT-PPCI study that suggested bleeding rates of heparin alone are not different from those of bivalirudin.[21]

4.2 In terms of the efficacy endpoint (major adverse cardiac events) our study findings is also compare able to several clinical trials.[20,25] Feit et al. have reported that QMI was 0.8% in bivalirudin arm and 1.6% in Heparin + GPI arm (p=0.05) but NQMI was 3.9% in bivalirudin arm and 4% in Heparin plus GPI arm (p=0.87) .[25]

In our study, there was no incidence of stent thrombosis and UTVR at all in the bivalirudin group as opposed to 3% in the UFH group and 2% in Heparin plus Eptifibatide group up to 30 days following stenting. Kaul et al. have reported no incidence of stent thrombosis and UTVR in the bivalirudin group in 30 days of PCI which is consistent with our study.[20] A recent study from China BRIGHT using bivalirudin protocol similar to our study also did not show any increase in in-stent thrombosis while maintaining lower bleeding rates 18. However, in MATRIX, HORIZONS-AMI and EURO MAX trial, patients treated with bivalirudin were at higher risk for acute stent thrombosis, an observation inconsistent with the results of our study.[22,26,27] The increased risk for acute stent thrombosis was limited to the first 4 h after the index procedure and was probably the result of the combination of the short half - life and rapid clearance of bivalirudin and the delayed bioavailability of the oral P2Y12 inhibitors, including the newer agents Prasugrel and Ticagrelor. Another reason for higher stent thrombosis in the EURO MAX study was the lower dose of bivalirudin infusion (0.25 mg/kg/hour) post procedure.[27]

In our study, in-hospital cardiac death rate was less in bivalirudin group as compared with UFH group (1% vs. 4 % ; p=0.36) & Heparin + Eptifibatide group (1% vs.2%; p=1.00). Cardiac death was absent in Bivalirudin arm but one cardiac death was found in two other groups in 30 days of PCI. Zhang et al. found similar results of death in a meta-analysis, where death was reported in 70 patients

assigned to the Bivalirudin and 92 patients assigned to the UFH group (RR=0.75; 95% CI 0.56-1.02; p=0.07).[15] Witzenbichler et al. have reported that the rates of cardiac death were significantly lower in patients treated with Bivalirudin compared with Heparin plus GPI in 30 days of PCI (2.1% vs. 5.5%, p = 0.04)26.The strength of our study was the absence of a sponsor for this study. However, further multicenter large randomized control trials would require to evaluate the exact incidence of MACEs and hemorrhagic complications of bivalirudin in ACS patients undergoing PCI by comparing currently used three different anticoagulation strategies like Heparin+GPI, bivalirudin and heparin monotherapy to generate evidence and future direction for Bangladeshi population.

Conclusion:

In this small scale, prospective, observational study of ACS patients undergoing PCI in a single-center showed that Bivalirudin is safer as it reduces hemorrhagic complications as compared to other contemporary antithrombotics. In terms of efficacy, Bivalirudin is superior to UFH monotherapy as it reduces MACEs and not inferior to Heparin plus Eptifibatde.

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