COMPARISON OF SAFETY AND EFFECTIVENESS OF BIVALIRUDIN BETWEEN DIABETIC AND NON-DIABETIC ACUTE CORONARY SYNDROME PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTION

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Abstract

Background: *Recurrent thrombotic events remain significantly high in spite of the currently recommended dual antiplatelet (DAPT) and conventional antithrombotic heparin (± GPI/ glycoprotein IIb/IIIa inhibitor) in diabetic ACS patients after PCI compared with non-diabetic even this drug eluting stent (DES) era. Therefore, more potent antithrombotic therapies are warranted for this group of high-risk patients.Comparison of safety and efficacy of newer anticoagulant bivalirudin between diabetic and non-diabetic ACS patients undergoing PCI using bivalirudin versus heparin (± GPI) is less well defined in Bangladeshi population.*

Objective: *To determine and compare the incidence of 30-day major adverse cardiac events (MACEs), stent thrombosis and hemorrhagic complications between diabetic and non-diabetic ACS patients undergoing PCI. Impact of antithrombotic strategy (bivalirudin vs. heparin ± GPI) on the 30- day post PCI clinical outcome was also evaluated and compared between diabetic and non-diabetic subgroup.*

Methods: *In this randomized controlled study, 500 ACS patients aged 18-75 years (200diabetic and 300 non-diabetics) who underwent PCI from November 2018 to October 2019 at the department of cardiology, BSMMU, were randomly assigned, in an open-label fashion to treatment with bivalirudin alone, heparin alone, or heparin plus eptifibatide (GPI) in a 1:1:1 ratio. Among them, 200 patients received Bivalirudin with a loading dose of 0.75 mg/kg, followed by an infusion of 1.75 mg/kg/h for up to 4 hours, 153 patients received UFH with a bolus of 70-100 U/kg (targeted ACT: 200-250 s) and 147 patients got heparin plus eptifibatide as 60 IU/kg heparin along with 180 µg/kg eptifibatide i.v. boluses, followed by a 2 µg /kg /min eptifibatide infusion for 18 hr consistent with current guidelines.Other pre- and post-procedural medications got under current guidelines. Both diabetic and non-diabetic subjects were subdivided into bivalirudin and control group (heparin ± GPI). In diabetic cohort, 100 patients were in bivalirudin and 100 patients were in control group. Among non -diabetic patients, 100 were in bivalirudin and 200 were in control group. The outcome measures were 30-day hemorrhagic complications, stent thrombosis, and MACCEs [death, MI, target lesion revascularization (TLR), and stroke] according to diabetic status. The diabetic and non-diabetic subgroup was also analyzed for the same outcome measure according to antithrombotic strategy. Peri and post PCI clinical follow-up comprised checking office visits and telephone contacts.*

Results: *According to diabetic status, net adverse clinical events (NACEs) were significantly higher in diabetic in comparison to non-diabetic (diabetic vs. non-diabetic, 15% vs. 7.6 %, P=0.008) and was associated with higher incidence of MACCEs (10.5% vs. 4.0%, P=0.004), cardiac death (4 % vs. 1 %, P=0.02) and BARC 2,3,5 grade bleeding events (9% vs. 4 %, P=0.02). In diabetic cohort, incidence of 30-day NACEs was significantly lower in bivalirudin than control group(bivalirudin vs. UFH ± GPI, 6 % vs. 24 %, P=0.004) and was associated with lower incidence of MACCEs (2% vs. 8.5%, P=0.03) and bleeding events (3 % vs. 15 %, P=0.003) whereas incidence of stent thrombosis (2 % vs. 3%, P =0.651) was comparable between the bivalirudin and control*

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groups. There was a significant advantage in favor of bivalirudin treatment among insulin-treated patients with regard to cardiac death at 30-day (bivalirudin vs. control group, 0% vs. 16.6%, p = 0.03) compared with non-insulin treat diabetic patients. However, subgroup analysis of the non-diabetic patients showed that there was no significant difference in the incidence of 30-Day NACEs (4% vs. 9.5%, P=0.09) according anticoagulant status. Multivariate analysis showed that bivalirudin (HR: 0. 202, 95% CI: 0.078 – 0.519, P=0.009) was independent protective factor of 30-day NACEs for diabetic patients.

Conclusion: *Bivalirudin monotherapy is safer and more efficacious for diabetic ACS patients compared with non-diabetic ACS patients undergoing PCI.*

Keywords: *ACS (Acute Coronary Syndrome), Bivalirudin, Diabetes mellitus (DM), PCI (Percutaneous Coronary Intervention).*

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Introduction

The world prevalence of diabetes mellitus (DM) among adults (aged 20–79 years) is predicted to rise to 7.7%, affecting 439 million adults by 2030.[1] Globally, diabetes is likely to be the fifth leading cause of death.[2] Coronary artery disease (CAD) resulting from accelerated atherosclerosis, is the leading cause of morbidity and mortality in patients with DM. Hence, DM has been classified as a coronary "risk equivalent".[3]

Coronary artery plaque rupture initiates acute coronary syndrome (ACS) by activating the platelet as well as coagulation cascade and thrombin plays the pivotal role in thrombus formation.[4] Effective and timely reperfusion of the infarct related coronary artery is central to optimal treatment for both STEMI (ST elevation myocardial infarction) and NSTE-ACS (NSTEMI/non ST elevation MI or UA/unstable angina) and is expeditiously and efficiently achieved by percutaneous coronary intervention (PCI).[5]

DM itself is a proinflamatory and prothrombotic state with enhanced thrombin generation, platelet reactivation, more pronounced vascular injury response and generally has a worse outcome after PCI compared with non-diabetic patients.[6] Recurrent thrombotic events remain significantly high in spite of the currently recommended dual antiplatelet (DAPT—Aspirin with P2Y12 inhibitor) and conventional peri-procedural antithrombotic (UFH / unfractionated heparin with or without GPI/ glycoprotein IIb/IIIa inhibitor) in diabetic ACS patients after PCI compared with non-diabetic even this drug eluting stent (DES) era. Therefore, more potent antithrombotic therapies are warranted for this group of high riskpatients.[7] However, prevention of hemorrhagic complications has emerged as apriority in patients undergoing PCI in addition to suppressing peri-procedural ischemia.

Intravenous (IV) UFH is traditionally regarded as the standard anticoagulant strategy during PCI though it has intrinsic limitation. UFH cannot inhibit thrombin without antithrombin-III or heparin cofactor-II. UFH binds to a number of plasma proteins, endothelial cells, vWF and macrophages, which reduces its anticoagulant activity, leads to heparin resistance. Relatively rapid clearance of UFH produces heparin rebound effect i.e. increased thrombin activity within a few hours after its cessation. So, UFH may cause heparin induced thrombo-cytopenia (HIT), unpredictable pharmacokinetics, nonlinear anticoagulant response with respect to peak effect and duration of action, a highly variable dose response relation, resulting in a narrow therapeutic window.[8-12] To overcome these limitations GPI invariably use with heparin during PCI which is costly and increases the risk of bleeding.[13]

Bivalirudin is a reversible IV direct thrombin inhibitor. It inhibits both circulating and clot bound thrombin as well as thrombin mediated platelet activation.[12] Numerous previous studies have reported that bivalirud inwitheffective anti-ischemic properties significantly reduces bleeding events in patients undergoing PCI.[6,16-18] Based on this evidence, bivalirudin is recommended as an alternative to UFH plus GPI during PCI in both STEMI[19]

and NSTE-ACS.[20] However, some studies that have compared heparin, heparin plus GPI and bivalirudin monotherapy yielded contradictory results with respect to ischemic, bleeding or combined outcomes.[21,22] Moreover, the impact of DM on the safety and effectiveness of bivalirudin in patients with ACS undergoing PCI is far from being clear.

In the current study, we tried to comparethe safety and efficacy of bivalirudinbetween diabetic and non-diabetic ACS patients undergoing PCI using bivalirudin versus heparin (with or without GPI Eptifibatide).

Method

Study population

In this randomized controlled study, 500 ACS patients (including STEMI within 12 hr after symptom onset or within 12–24 hr with ongoing chest pain, ST-segment elevation or new left bundle branch block, and NSTE-ACS within 72 hr after symptom onset) aged 18–75 years who underwent PCI from May 2018 to April 2019 at department of cardiology, BSMMU, Dhaka were enrolled after exclusion of the following criteria:cardiogenic shock; thrombolytic therapyadministered before randomization or any anticoagulant administered within 8 hr of randomization (however, prior UFH allowed) ; active or recent major bleeding or bleeding predisposition; major surgery within 1 month; clinical syndrome suggestive of aortic dissection, pericarditis, or endocarditis; blood pressure higher than 180/110 mm Hg; known hemoglobin levels less than 10 g/dl, platelet counts less than 100 X 10^9/L, aminotransferase levels greater than 3 the upper limit of normal, or Creatinine clearance less than 30 mL/min; history of HIT; allergy to any of the study drugs or devices; pregnancy or lactation; using bare metal stent(BMS) during PCI, any condition making PCI unsuitable or that might interfere with study adherence; and patient unwillingness or inability to provide written informed consent. Informed written consent was taken from patients or next of kin. Prior ethical approval was obtained from the ethical review committee of BSMMU.

The study protocol (Randomization and Treatment)

After the choice had been made to perform a coronary intervention, 500 ACS patients were randomly assigned, without stratification by STEMI vs. NSTE-ACS or by DM vs. Non-DM, in an open-label fashion to treatment with bivalirudin alone, heparin alone, or heparin plus eptifibatide (GPI) in a 1:1:1 ratio. Before the guide wire crossed the lesion, 200 patients received Bivalirudin with a loading dose of 0.75 mg/kg, followed by an infusion of 1.75 mg/kg/h for up to 4 hours, 153 patients received UFH with a bolus of 70-100 U/kg (targeted ACT: 200-250 s) and 147 patients got heparin plus eptifibatide as 60 IU/kg heparin along with 180 µg/kg eptifibatide i.v. boluses, followed by a 2 µg /kg /min eptifibatide infusion for 18 hr consistent with current guidelines.[23] Provisional (bailout) eptifibatide use was allowed in the bivalirudin and heparin-only groups for no-reflow or other thrombotic complications. 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 a minimum of 2 hours before PCI. Other pre- and post-procedural medications got under current guidelines. Coronary angiogram (CAG) and PCI were performed by respective consultants according to current practice guideline. Decisions regarding the choice of access siteand stent type were at operator discretion consistent with local standards of care.Two experienced cardiologists who were blinded to patient information reviewed the cine angiograms. Less than thirty percent (<30%) residual stenosis and TIMI grade 3 flow after the procedure were counted as successful PCI. DES was used for every patient. Peri and post PCI clinical follow-up comprised checking office visits and telephone contacts.

Study End-points and Definition

The outcome measures were 30-day hemorrhagic complications, stent thrombosis, and major adverse cardiovascular or cerebral events (MACCEs). The diabetic and non-diabetic subgroup was also analyzed for the same outcome measure according to antithrombotic randomization. The primary end-point was the incidence of net adverse clinical events (NACEs) at 30 days, a composite of MACCEs [all-cause death including cardiac and non-cardiac death,

reinfarction/new MI/non-fatalACS, ischemia driven target vessel/lesionrevascularization (TVR/TLR), or stroke]or bleeding as defined by the Bleeding Academic Research Consortium (BARC) definition (grades 2, 3, 5) [24]. NACEs, a term first introduced in the HORIZONS-AMI trial, were defined as the combination of major bleeding and a composite of MACE.[16] Non-cardiac death was defined as a death not due to cardiac causes, including bleeding related death. UnplannedTVR was defined as the first future revascularization (by CABG or repeat PCI) after the index procedure. TLR was defined as repeat revascularization clinically driven (recurrence of chest pain and new ECG changes) by any lesion in a stented segment (e" 50% diameter stenosis with e" 5 mm proximal or distal to the DES).[25] Additional predefined safety end-points included stent thrombosis at 30 days, consistent with the Academic Research Consortium criteria[26], and acquired thrombocytopenia at 30 days, defined as a decrease in platelet count of more than 50% or more than 150 x 109/L from baseline.

Statistical analysis:

Statistical analyses wereplanned and reviewed by the investigators and guide.After editing, data analysis was carried out by using the Statistical Package for Social Science (SPSS)version 23.0 windows software. Data were statistically described in terms of mean ± standard deviation (±SD), or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student t test for independent samples. For comparing categorical data, Chi square test was performed. Fisher's exact correction was used when the expected cell count is less than 5. Outcome data for the primary and secondary end-points were compared as binary proportions. Multivariate analysis was performed usinga Cox proportional hazard model. The levelof significance for all analytical tests was set at 0.05 and a p-value less than 0.05 is taken into account significant.

Result:

The present study, intended to compare the safety and efficacy of bivalirudin between diabetic and non-diabetic ACS patients within 30 day after PCI, included 500 consecutive ACS patients (200 diabetic and 300non-diabetics) who underwentPCI. Among diabetic patients, 54 (27%) treated with insulin and 146(73%) treated with oral hypoglycemic medications without insulin. After randomization according to anticoagulant,both diabetic and non-diabetic subjects were subdivided into bivalirudin (peri-procedural anticoagulant was bivalirudin) and control group (patients got UFH with or without GPI Eptifibatide during PCI). In diabetic cohort, 100 patients were in bivalirudin and 100 patients were in control group. Among non - diabetic patients, 100 were in bivalirudin and 200were in control group. The outcome measures were 30-day NACEs, MACEs, BARC 2,3,5 grade bleeding and stent thrombosis.The findings of the study obtained from data analyses are documented below:

Patients and procedures

There were several significant differences in baseline characteristics between diabetic and non-diabetic patients. Compared with non-diabetic patients, diabetic patients were younger (diabetic vs. non-diabetic, 55.4 ± 11.6 vs. 57.9 ± 11.8, P=0.01), had a higher body mass index (26.2 ± 3.9 vs. 25.4 ± 3.6, P=0.01) and had a higher incidence of comorbidities such as hypertension (68 % vs. 52 %, P=0.0004), hyperlipidemia (53 % vs. 39 %, P=0.002) and renal insufficiency (Creatinine clearance d"60 ml/min, 19% vs. 11 %, P=0.01). The average CRUSADE bleeding score was higher in diabetic in comparison with non-diabetic patients (33.4 ± 6.0 vs. 20.5 ± 12.2, P< 0.0001) (Table I).

Data from 200 diabetic patients enrolled in the current study were analyzed, including 100 patients randomized to the bivalirudin group and 100 patients randomized to the control group (UFH ±GPI eptifibatide). In the diabetic subgroup, the activated clotting time (ACT) of the bivalirudin group was markedly prolonged compared with that of the control group (P<0.0001). There were no other significant differences in baseline characteristics or other medical characteristics between the bivalirudin group and the control group (Tables III and IV).

Data on 300 non-diabetic patients enrolled in the current study were also analyzed, including

100 patients randomized to the bivalirudin group and 200 patients randomized to the control group (patient UFH ±GPI). In the non-diabetic subgroup, ACT of the bivalirudin group was markedly prolonged compared with that of the control group (P<0.0001). No other significant differences in baseline characteristics or other medical characteristics were identified between the study group (Table III and IV).

Clinical Outcomes

Comparisons of event rates between the diabetic and non-diabetic groups are shown in Table III. The primary outcome NACE was significantly higher in diabetic patients than in non-diabetic patients (diabetic vs. non-diabetic, 15 % vs. 7.6 %, P=0.008) and was accompanied by markedly higher incidence of MACCEs (10.5 % vs. 4.0 %,P = 0.004), all-cause death (4.5 % vs. 1.3 %, P= 0.02), cardiac death (4 % vs. 1 %, P= 0.02), ischemic TVR (3% vs. 0.6%, p=0.03) and BARC 2,3,5 grade bleeding events (9 % vs. 4 %, P= 0.02) in diabetic cohort than in non-diabetic cohort. No significant differences between the diabetic and non-diabetic groups were observed for the other clinical endpoints, as shown in Table II.

Table I

Baseline Characteristics and Treatment Strategies according to Diabetic Status

Characteristics	Diabetic Patients (n=200)	Non-Diabetic patients (n=300)	p-Value
Age, years, mean (SD)	55.4 ± 11.6	57.9 ± 11.8	a0.019s
Female, n (%)	72 (36)	81 (27)	b0.032s
Body mass index, BMI (kg/m^2)mean (SD)	26.2 ± 3.9	25.4 ± 3.6	a0.019s
Medical history-Co morbidity			
Hypertension, n (%)	136 (68)	156 (52)	b0.0004s
Current smoker, n (%)	36 (18)	99 (33)	b0.0002s
Hyperlipidemia, n (%)	106(53)	117(39)	b0.002s
Previous Myocardial infarction (MI), n (%)	34(17)	27 (9)	b0.007s
Prior coronary Intervention, n (%)	22 (11)	15 (5)	b0.012s
Previous Stroke (no TIA), n (%)	12(6)	6(2)	b0.018s
Clinical Presentation			
STEMI	82(41)	90(30)	b0.011s
NTSE-ACS (NSTEMI+UA), n (%)	118(59)	210(70)	b0.011s
Symptom onset to hospital arrival, hour	9.2 ± 2.8	8.8 ± 3.2	a0.151ns
Clinical Risk assessment			
Killip class e”II, n (%)	24 (12)	21 (7)	b0.055ns
Anemias¦, n (%)	30 (15)	24 (8)	b0.013s
Thrombocytopenia ¥, n (%)	11(5.5)	8(2.6)	b0.095ns
Renal insufficiency*, n (%)	38(19)	33(11)	b0.012s
LVEF>40%, n (%)	172(86)	276(92)	b0.031s
CRUSADE bleeding score, mean (SD)	33.4 ± 6.0	20.5 ± 12.2	b< 0.0001s
CRUSADE bleeding score >30	114(57)	33 (11)	b< 0.0001s
Treatment Strategy			
Primary PCI	36 (18)	51 (17)	a0.772ns
Early invasive (<24 h) strategy for NSTE-ACS	90 (45)	129 (43)	a0.659ns

CRUSADE denotes Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines, s¦ Anemia was defined as Hematocrit value at initial presentation<39% for men and <36% for women (or, hemoglobin levels < 12 g/dL for men or < 11 g/dL for women)., ¥ Platelet <150,000 cells/mm^3*Creatinine clearance d” 60 mL/min, S=significant, ns=not significant, a =P value from unpaired t-test, b =Pvalue from Chi-square test.

Subgroup analysis of diabetic patients showed that the incidences of 30-day NACEs was significantly lower in the bivalirudin group than in the control group (Bivalirudin vs. Control, 6.0% vs. 24%, P =0.004) and was accompanied by markedly lower incidence of MACCEs (2 % vs. 8.5 %, P = 0.03), all-cause death (1 % vs. 8 %, P= 0.01), cardiac death (1 % vs. 7 %, P= 0.03), and BARC 2,3,5 grade bleeding events (3 % vs. 15 %, P= 0.003) in bivalirudin group than in the control group.The incidence of stent thrombosis (2 % vs. 3%, P =0.651) was comparable between the bivalirudin and control groups (Table V).

However, Subgroup analysis of non-diabetic patients showed that the incidence of 30-day NACEs, MACEs, BARC 2, 3, 5 grade bleeding event and stent thrombosis were not significantly different between the bivalirudin and control group (Table V).

Further analysis of the diabetic patients according to insulin-treated and noninsulin-treated cohorts revealed that the incidence of NACEs was remarkably different between the bivalirudin and the control group (p<0.05), whereas there was a significant advantage in favor of bivalirudin treatment among insulin-treated patients with regard to all cause death and cardiac death at 30-day (bivalirudin vs. control group, 0% vs. 16.6%, p = 0.03)(Table VI).

Multivariate analysis showed that bivalirudin (odds ratio [HR]: 0.202, 95% confidence interval [CI]: 0.078–0.519, P=0.0009), trans-radial access (HR: 0.323, 95% CI: 0.117–0.886, P =0.028), and statin (HR: 0.250, 95% CI: 0.083–0.750, P = 0.013) were independent protective factors for 30-day NACEs in diabetic patients. Hypertension (HR: 3.545, 95% CI: 1.181–10.637, P= 0.02) and renal insufficiency (HR: 2.535, 95% CI: 1.072–5.995, P=0.03) were independent risk factors of 30-day NACEs.DAPT (Aspirin + Ticagrelor) (HR: 0.292, 95% CI: 0.112–0.760, P = 0.01) was an independent protective factor, whereas female sex (HR: 3.305, 95% CI: 1.298–8.412, P=0.01) and Hyperlipidemia (HR: 3.164, 95% CI: 1.111–9.007, P = 0.03) was an independent risk factor for 30-dayMACCEs in diabetic patients (Table VII).

Table II

Clinical outcome at 30 days according to diabetic status

Events, n (%)	Diabetic patients (n=200)	Non-diabetic patients (n=300)	p Value
NACEs (Net adverse clinical events)	30 (15)	23 (7.6)	0.008^{S}
MACCEs (Major adverse cardiac or cerebral events)	21 (10.5)	12(4)	0.004^{S}
Death(all-cause)	9(4.5)	4 (1.3)	0.027^{S}
Cardiac death	8(4.0)	3(1.0)	0.025^{S}
Reinfarction (non-fatal new MI)	6 (3)	7(2.3)	0.629ns
Stroke	2(1.0)	2 (0.6)	0.614ns
Ischemic TVR	6 (3.0)	2(0.6)	0.034^{S}
All Bleeding* (*BARC 2,3,5 type bleeding)	**18 (9)**	**12 (4)**	**0.021^{S}**
Additional safety end point			
Thrombocytopenia	4(2)	2(0.6)	0.152ns
Stent thrombosis	5(2.5)	7(2.3)	0.885ns
Definite	3(1.5)	3(1.0)	0.615ns
Probable	2(1.0)	4(1.3)	0.761ns
Acute (<24 hr.)	2(1.0)	3(1.0)	1.00ns
Sub-acute (1–30 days)	3(1.5)	4(1.3)	0.851ns

S=significant, ns=not significant

Table III

Baseline Characteristics of Diabetic and Non-diabetic patients according to Randomized Treatment Group

Characteristics	Diabetes			No Diabetes		
	Bivalirudin (n=100)	Control * (Heparin ±GPI) (n=100)	p-Value	Bivalirudin (n=100)	Control* (Heparin ±GPI) (n=200)	p-Value
Age, years, mean (SD)	55.4 ± 11.4	54.6 ± 10.2	0.601	57.8 ± 11.7	56.7 ± 9.8	0.391
Female, n (%)	34 (34)	38(38)	0.556	25 (25)	56(28)	0.581
BMI (kg/m2) mean (SD)	26.2 ± 3.5	25.9 ± 3.7	0.556	25.6 ± 3.2	24.9 ± 3.4	0.087
Medical history						
Hypertension, n (%)	64 (64)	72 (72)	0.226	56 (56)	100 (50)	0.327
Current smoker, n (%)	16 (16)	20 (20)	0.462	35 (35)	64 (32)	0.603
Hyperlipidemia (%)	55 (55)	51 (51)	0.571	41 (41)	76(38)	0.616
Previous MI, n (%)	18 (18)	16(16)	0.707	10 (10)	17(8.5)	0.669
Prior coronary intervention, n (%)	12 (12)	10(10)	0.652	6 (6.0)	9(4.5)	0.574
Previous Stroke, n (%)	7 (7)	5 (5)	0.552	2 (2.0)	4(2.0)	1.00
Clinical Presentation						
STEMI, n (%)	42 (42)	40(40)	0.774	32 (32)	58(29)	0.593
NTSE-ACS (NSTEMI+UA), n (%)	58(58)	60(60)	0.774	72 (72)	138 (69)	0.593
Symptom onset to hospital arrival, hour	9.5 ± 2.9	9.0 ± 2.7	0.208	8.7 ± 3.1	8.9 ± 3.3	0.614
Insulin-treated diabetes	24(24)	30(30)	0.340	-	-	-
Clinical Risk assessment						
Killip class ≥II, n (%)	13 (13)	11(11)	0.664	6 (6)	15 (7.5)	0.631
Anemias¦, n (%)	16 (16)	14(14)	0.692	10 (10)	14(7)	0.367
Renal insufficiency*, n (%)	20 (20)	18 (18)	0.719	13(13)	20(10)	0.434
LVEF>40%, n (%)	84 (84)	88 (88)	0.416	90 (90)	186 (93)	0.367
HbA1C, mean (SD)	8.9 ± 1.5	8.7 ± 1.8	0.394	-	-	-
CRUSADE bleeding score, mean (SD)	33.1 ± 6.1	32.9 ± 5.8	0.812	20.8 ± 9.8	20.6 ± 11.1	0.878

*control group = patients randomized to UFH with or without Eptifibatide (GPI), *Creatinine clearance d" 60 mL/min, LVEF=Left ventricular ejection fraction, s¦Anemia was defined as Hematocrit value at initial presentation<39% for men and <36% for women (or, hemoglobin levels < 12 g/dL for men or < 11 g/dL for women). CRUSADE denotes Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/ AHA guidelines.

Table IV

Procedure and Medication of Diabetic and Non-diabetic patients according to Randomized Treatment Group

Characteristics	Diabetes			No Diabetes		
	Bivalirudin (n=100)	Control* (Heparin ±GPI), (n=100)	p-Value	Bivalirudin (n=100)	Control* (Heparin ±GPI), (n=200)	P-Value
Arterial access, n (%)						
Trans femoral	68 (68)	62(62)	0.374	66(66)	134(67)	0.862
Trans radial	34(34)	36(36)	0.374	34(34)	66(33)	0.862
Severity of disease, n (%)						
Single vessel disease	55(55)	53(53)	0.777	59(59)	124(62)	0.616
Double vessel disease	36(36)	39(39)	0.662	36(36)	68(34)	0.731
Triple vessel disease	9(9.0)	8(8.0)	0.800	5(5)	8(4)	0.688
Lesion characteristic, n (%)						
Type A	60(60)	58(58)	0.774	62(62)	122(61)	0.867
Type B	37(37)	38(38)	0.884	37(37)	75(37.5)	0.932
Type C	3(3)	4(4)	0.701	1(1.0)	3(1.5)	0.722
DAPT before randomization, n (%)						
Aspirin+ Ticagrelor	61(61)	59(59)	0.773	59(59)	120(60)	0.868
Aspirin + Prasugrel	14(14)	8(8)	0.176	10(10)	18 (9)	0.779
Aspirin +Clopidogrel	25(25)	33(33)	0.213	31(31)	62 (31)	1.00
Culprit vessel treated - PCI, n (%)						
Left anterior descending	52(52)	51(51)	0.887	54(54)	110(55)	0.869
Left circumflex	23(23)	24(24)	0.867	21(21)	40(20)	0.839
Right coronary artery	24(24)	25 (25)	0.869	23(23)	47(23.5)	0.923
Left main coronary artery	1(1.0)	0(0.0)	0.317	2(2.0)	3(1.5)	0.750
ACT ¥, seconds	319.2±102.6	265.7±67.4	<0.0001	319.4±101.4	267.3±68.7	<0.0001
Mean vessel diameter, mm	2.92±0.6	2.91±0.8	0.920	2.92±0.5	2.93±0.3	0.829
Number of stents per patient	1.13±0.5	1.12±0.4	0.876	1.10 ±0.2	1.11±0.3	0.763
Mean stent length, mm	28.24±10.12	29.01±9.8	0.585	27.14±10.7	27.94±10.5	0.536
TIMI FLOW (Pre PCI), n (%)						
0/1	81	80	0.563	79(79)	160(80)	0.839
2	10	12	0.652	12(12)	25(12.5)	0.901
3	9	8	0.800	9(9.0)	15(7.5)	0.652
TIMI FLOW (Pre PCI), n (%)						
0/1	2	2	1.00	2(2.0)	5(2.5)	0.787
2	3	4	0.701	2(2.0)	5(2.5)	0.787
3	95	94	0.757	96(96)	190(95)	0.699
Medication at discharge, n(%)						
*DAPT (*Aspirin+ Ticagrelor)	62(62)	58(58)	0.564	60(60)	122(61)	0.867
DAPT (Aspirin + Prasugrel)	11(11)	9 (9)	0.638	13(13)	22(11)	0.611
DAPT(Aspirin +Clopidogrel)	27(27)	31(33)	0.355	27(27)	56(28)	0.855
Statin	94(94)	90(90)	0.298	89(89)	180(90)	0.788
Beta-blockers	79(79)	81(81)	0.724	78(78)	155(77.5)	0.922
ACE-inhibitors or ARB	59(59)	63(63)	0.563	58(58)	119(59.5)	0.803

¥ Activated clotting time (ACT) was recorded 5 min after bolus of anticoagulant during PCI.*control group denotes patients randomized to UFH with or without Eptifibatide (GPI)

Table V

30-Day Clinical outcome of Diabetic and Non-diabetic patients according to Randomized Treatment Group

Characteristics	Diabetes			No Diabetes		
	Bivalirudin (n=100)	Control* UHH±GPI (n=100)	p-Value	Bivalirudin (n=100)	Control* UHH±GPI (n=200)	p-Value
NACEs	6(6)	24(24)	0.004	4(4.0)	19(9.5)	0.092
MACCEs	4(2)	17(8.5)	0.039	3(3.0)	9(4.5)	0.532
All-cause death	1(1)	8(8)	0.017	1(1)	3(1.5)	0.722
Cardiac death	1(1)	7(7)	0.030	1(1)	2(1.0)	1.00
Reinfarction	2(2)	4(4)	0.408	2(2)	5(2.5)	0.787
Stroke	1(1)	1(1)	1.00	0(0)	2(1.0)	0.316
Ischemic TVR	1(1)	5(5)	0.098	0(0)	2(1.0)	0.316
All Bleeding -BARC 2,3,5 type	3(3)	15(15)	0.003	1(1)	11(5.5)	0.061
Additional safety end point						
Thrombocytopenia	0(0)	4(4.0)	0.043	0(0)	2(1.0)	0.316
Stent thrombosis	2(2.0)	3(3.0)	0.651	2(2.0)	5(2.5)	0.787
Definite	1(1.0)	2(2.0)	0.561	1(1.0)	2(1.0)	1.00
Probable	1(1.0)	1(1.0)	1.00	1(1.0)	3(1.5)	0.722
Acute (<24 hr.)	1(1.0)	1(1.0)	1.00	1(1.0)	2(1.0)	1.00
Sub-acute (1–30 days)	1(1.0)	2(2.0)	0.561	1(1.0)	3(1.5)	0.722

*control group =patients received UFH with or without Eptifibatide, MACCEs denotes Major adverse cardiac or cerebral events,NACEs denotes Net adverse clinical events.

Table VI

30-Day Clinical outcome of Diabetic patients according to Insulin treatment

Characteristics	Insulin treated Diabetes (54)			Non-Insulin treated Diabetes (146)		
	Bivalirudin (n=24)	Control* UHH±GPI (n=30)	p-Value	Bivalirudin (n=70)	Control* UHH±GPI (n=76)	p-Value
NACEs	1(4.1)	9 (30)	0.015	5(7.1)	15 (19.7)	0.027
MACCEs	1(4.1)	7(23.3)	0.050	3(4.3)	10(13.1)	0.062
All-cause death	0(0)	5(16.6)	0.037	1(1.4)	3(3.9)	0.353
Cardiac death	0(0)	5(16.6)	0.037	1(1.4)	2(2.6)	0.608
All Bleeding -BARC 2,3,5 type	1(4.1)	7(23.3)	0.050	2(2.8)	8(10.5)	0.065
Stent thrombosis	1(4.1)	1(3.3)	0.877	1(1.4)	2(2.6)	0.608

Table VII

Independent Predictors of Adverse Clinical Events by Multivariate Analysis in Diabetic patients

Predictors	HR (95% CI)	*P*-value
Predictors of NACEs		
Bivalirudin use	0.202 (0.078 to 0.519)	0.0009
Trans radial access	0.323 (0.117 to 0.886)	0.028
Discharge medication -Statin	0.250 (0.083 to 0.750)	0.013
Hypertension	3.545 (1.181 to 10.637)	0.024
Renal insufficiency	2.535 (1.072 to 5.995)	0.034
Predictors of MACEs		
Female sex	3.305 (1.2985 to 8.412)	0.012
Hyperlipidemia	3.164 (1.111 to 9.007)	0.030
Discharge medication -DAPT (Aspirin + Ticagrelor)	0.292 (0.112 to 0.760)	0.011

Discussion

In the present study, diabetic patients showed worse clinical baselines and higher rates of NACEs and MACCEs at 30 days compared with non-diabetic patients, consistent with previous studies.[7,27]

Regarding diabetic patients, our study revealed that patients randomized to bivalirudin rather than heparin± GPI benefitted from a pronounced reduction in bleeding events, along with NACEs and all cause and cardiac mortality. In terms of the safety endpoint (bleeding risk) our study findings are consistent with previous literature. In a meta-analysis, Zhang et al. have reported that bivalirudin decreases the risk of major bleeding more significantly than heparin (174 DM patients in bivalirudin vs. 297 DM patients in heparin group experienced major bleeding: RR 0.63; 95% CI 0.52-0.75; P<0.00001).[6] Nairooz et al. concluded that bivalirudin reduces major bleeding risk significantly in diabetic ACS patients following PCI (OR 0.68; 95% CI 0.52- 0.89; P=0.005).[18] Feit et al. have reported that major bleeding was 3.7% in bivalirudin arm and 7.1% in Heparin +GPI arm (p<0.001).[28] In terms of the efficacy endpoint (MACCEs) our study findings are also comparable to previous study done by Witzenbichler et al. (2011) and Feit et al. (2008).[28,29] The difference in protocols and operative definitions of post PCIMI and routine use of GPI with heparin is the reason for alittle discrepancy in the incidence of different component of MACCEs between our results and other real-world data.Our study also showed that compared with non-insulin treated diabetic patients bivalirudin significantly reduces the incidence of cardiac death in insulin treated diabetic patients,which is consistent with previous studies.[28,29] In terms of stent thrombosis, previous studies have suggested a higher rate of stent thrombosis in diabetic patients, particularly those insulin-treated.[30,31] In the present analysis the overall rate of stent thrombosis in the diabetic subgroup was comparable in patients treated with bivalirudin or those treated with heparin± GPI. 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.[17] 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. Routine use of post PCI 4-hour infusion of bivalirudin in our study might be the reason for lower incidence of stent thrombosis.

Regarding non-diabetic patients, our study revealed that in terms of safety (bleeding risk), efficacy (MACCEs), stent thrombosis and overall

incidence of NACEs was not significantly different between bivalirudin and conventional antithrombotic heparin± GPI, which is in agreement with the results of previous studies of the overall population**.** Shahzadet al (2014) and Leonardi et al (2016)have similarly reported that bivalirudin is comparable with UFH (with or without GPI).[21,22]

Conclusion

Diabetic ACS patients undergoing PCI have worse outcomes, in terms of both ischemic events and bleeding complications, compared with nondiabetic patients, despite contemporary antithrombin and antiplatelet therapy. Among diabetic patients, treatment with bivalirudin monotherapy rather than a heparin-based regimen (with or without GPI eptifibatide) significantly reduces net adverse clinical outcomes by providing more protection from ischemic events and significantly reducing major bleeding complications as well. The benefits of bivalirudin monotherapy were maintained in patients treated with insulin. Bivalirudin monotherapy is safer and more efficacious for diabetic ACS patients compared with non-diabetic ACS patients undergoing PCI.

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