Original Article
Bivalirudin is associated with better clinical outcomes as opposed to unfractionated heparin in patients undergoing primary percutaneous coronary intervention

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Abstract: *Objectives:* Prevention of adverse ischemic events during and after primary percutaneous coronary intervention (PCI) in patients with acute myocardial infarction (AMI) is the essential role of antithrombotic therapy. The clinical outcomes and efficacy of these antithrombotic agents should be weighed in against their relative risks of hemorrhagic complications. The aim of this study was to compare the effect of bivalirudin with unfractionated heparin (UFH) anticoagulant therapies in patients with AMI undergoing primary PCI and to elucidate their clinical prognostic significance. *Materials and methods:* We performed a prospective, open label multicenter trial in which patients with AMI undergoing primary PCI were randomized to bivalirudin or heparin alone. A total of 459 patients were consecutively enrolled between June 2013 and July 2015. The anti-thrombotic strategy was decided upon by the operator. Patient age ranged from 18 to 80 years. The patients were admitted with AMI within 12 hours after symptom onset or within 12 to 24 hours with ongoing chest pain, with ST-segment elevation, or with a new left bundle branch block, and consequently underwent primary PCI with an approved device. Patients were assigned to 2 cohorts. The first group received bivalirudin as a bolus of 0.75 mg/Kg followed by an infusion of 1.75 mg/Kg/h during the PCI procedure for a median of 3 hours. The second group received UFH monotherapy as an intravenous bolus of 100 IU/Kg, according to the current guidelines, with subsequent boluses targeted to an activated clotting time (ACT) of >200 seconds. *Results:* The incidence of stroke (hemorrhagic) and stent thrombosis were similar in both the bivalirudin and heparin cohorts (0.9 *vs.* 2.97% and 0.9 *vs.* 1.27%, respectively). There was however a significant difference in the all-cause bleeding cases in the bivalirudin arm as opposed to the heparin arm (5.38 *vs.*13.98%; relative risk [RR] for bivalirudin *vs.* heparin, 0.3848; 95% CI=0.2039-0.7262; P=0.002). Nine patients (4.04%) treated with bivalirudin while 25 (10.59%) treated with heparin only, experienced a statistical significant difference in all bleeding events (including access and non-access sites) at the primary 30-day endpoint (relative risk [RR]=0.3810; 95% CI=0.1818-0.7983), *P*=0.0073). The rates of major adverse cardiac or cerebral events (4.48% *vs.* 9.32%; RR=0.4329; 95% CI=0.2037-0.9200, *P*=0.0241) and its individual components were also statistically significant between the 2 groups. In addition, there was a statistically significant difference in the rates of severe bleeding in the bivalirudin *vs.* heparin cohorts (0.45% *vs.* 5.51%; RR=0.0814; 95% CI=0.01073-0.6175, *P*=0.0016) after 30 days. *Conclusion:* We put forward that bivalirudin was associated with significant reductions in all-cause bleeding, severe bleedings and major adverse coronary and cerebral events (MACCE) following prolonged hospitalization (30 days). The use of bivalirudin further cements its role as a novel and potent anti-thrombin drug, greatly superior to heparin.

Keywords: Primary percutaneous coronary intervention (PCI), acute myocardial infarction (AMI), unfractionated heparin (UFH), activated clotting time (ACT)

Introduction

Prevention of adverse ischemic events, notably stent thrombosis and reinfarction during and after primary percutaneous coronary intervention (PCI) in patients with acute myocardial infarction (AMI) is the essential role of anti-thrombotic therapy [1-4]. The clinical outcomes and efficacy of these noble antithrombotic agents should be weighed in against their relative risk of hemorrhagic complications, which could undoubtedly lead to subsequent increased mortality and morbidity [5-8].

Unfractionated heparin (UFH) has been the cornerstone of anticoagulant therapy during percutaneous coronary intervention (PCI) over the past two decades. Yet, there are limitations in its unpredictable pharmacodynamics (it requires a cofactor), plasma protein inhibition, and its potential to activate platelets [9-12]. UFH is also highly antigenic. It develops a variable degree of resistance and also causes adverse effects such as heparin induced thrombocytopenia and thrombosis syndrome (HIT/TS) in 1 to 2% of patients [13].

Bivalirudin is a reversible direct thrombin inhibitor with a relatively short half-life and its elimination is independent of renal or hepatic functions. Several trials have favored and advocated the use of bivalirudin as a replacement for heparin in patients undergoing PCI [14-16]. Several clinical trials and meta-analyses have also shown that the use of bivalirudin is associated with a significant reduction in complications related to bleeding in patients undergoing PCI [17-21] with notable, yet insignificant reductions achieved with a Post-PCI infusion. This was demonstrated in the Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of angiox (MATRIX) and Bivalirudin in Acute Myocardial Infarction vs. Heparin and GPI Plus Heparin (BRIGHT) trials [22, 23]. Subsequently, due to increasing evidence favorable to the use of bivalirudin in patients undergoing PCI, it has inherently received a class-I recommendation as an anticoagulant for PCI [24, 25]. Due to apparent discrepancies in the results, the safety and efficacy of bivalirudin in patients with AMI undergoing PCI remain uncertain, especially when compared to heparin alone. Subsequently, we performed a prospective, open label multicenter trial in which patients with AMI underwent primary PCI with bivalirudin or heparin alone. Various clinical trials, such as the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) [26], the European Ambulance Acute Coronary Syndrome Angiography (EUROMAX) [27, 28], the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE-2) [16], and the recently concluded BRIGHT [23], have shown that procedural anticoagulation with bivalirudin is associated with statistically significant reductions in 30-day major bleeding, and correspondingly notable reductions in net adverse clinical events. The HORIZONS-AMI also showed a sustained mortality reduction for a period of 3 years [26]. These findings were however associated with an increased rate of acute stent thrombosis, which was further validated in the How Effective are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention (HEAT-PPCI) trial. It demonstrated increased 30-day rates of stent thrombosis and reinfarction with bivalirudin (without a post-PCI infusion) as compared to heparin alone, with no difference in bleeding [29].

All these trials warrant a more extensive look into anticoagulant efficacy, bleeding reductions, major adverse effects, and rates of acute stent thrombosis of these two novel anticoagulant drugs.

Materials and methods

Patient selection

We ran a prospective, multicenter, open-label, observational study to demonstrate whether bivalirudin administration was associated with better outcomes in relation to bleeding reductions than Unfractionated Heparin (UFH) in patients with AMI undergoing primary PCI.

Between June 2013 and July 2015, 639 patients were included in this prospective study. Patients were selected from the Shandong Provincial Hospital, Central Hospital of Tai'an, Dongying People's Hospital, Zibo City Central Hospital, and Qingzhou City People's Hospital. The choice of anti-thrombotic strategy was left to the discretion of the individual operator(s), which was based on their own clinical judgment and on patient's affordability. Patients were eligible for inclusion if they were aged between 18 and 80 years, presenting with AMI, including anterior, inferior or anterior + inferior MI within 12 hours after symptom onset or within 12 to 24 hours with ongoing

Table 1. Baseline characteristics of 459 patients with AMI undergoing PCI

Characteristic		Bivalirudin (n=223)	Heparin (n=236)
Gender	Male	161 (72.2)	172 (72.88)
	Female	62 (27.8)	64 (27.12)
Age, mean (SD), y		5416	5619
Diabetes No. (%)		36 (16.1)	40 (16.9)
Hypertension		139+21/87+13	138+19/88+11
LDL-c (mmol/dl)		3.9+0.7	3.9+0.9
Anterior MI, No. (%)		137 (61.43)	156 (66.10)
Inferior MI, No. (%)		64 (28.70)	56 (23.73)
Anterior + Inferior MI, No. (%)		22 (9.87)	24 (10.17)

Abbreviations: LDL-c: low-density lipoprotein-c; MI: myocardial infarction.

chest pain, with ST-segment elevation or with a new left bundle branch block, and consequently underwent primary PCI with an approved device. Exclusion criteria included contraindication to any of the study medications, cardiogenic shock, uncontrolled hypertension (blood pressure >180/110 mmHg), prior or planned staged PCI within the preceding or following month, pregnancy or lactation, history of major surgery within one month, active or recent major bleeding or bleeding diathesis (gastrointestinal, genitourinary tract, prior intracrnial bleeding or structural abnormality), known hemoglobin <10 g/dL, platelet count <100×10^9/L, renal insufficiency (CCR<30 mL/min), aminotransferase level >3× the upper limit of normal values and any condition resulting in unsuitable PCI or possible interference with study adherence, and patient unwilling or unable to provide written informed consent and unable to collect follow-up. Patient's criteria which did not match the inclusion criteria were excluded from the study group. Furthermore, patients without available data and follow-up were excluded. Consequently, after exclusion, a total of 459 eligible patients were enrolled in our study. The study protocol was approved by the Committee on the Ethics of Human Research at each clinical site, and complied with the principles of Helsinki's declaration. Written informed consents were obtained from all participants.

Study protocol

Patients were assigned to 2 cohorts depending on the choice of anti-thrombotic therapy. Patients were administered the study medications prior to angiography in the catheterization laboratory. The first group received bivalirudin (Shenzhen Salubris Pharmaceuticals, Guangdong, PRC) as a bolus of 0.75 mg/Kg followed by an infusion of 1.75 mg/Kg/h during the PCI procedure for a median of 3 hours. An additional bivalirudin bolus of 0.3 mg/Kg was administered when ACT was >225 seconds. The second group received unfractionated heparin monotherapy as an intravenous bolus of 100 IU/Kg according to the current guidelines with subsequent boluses targeted to an ACT>200 seconds. ACT was measured with the HemoTec assay, and 5 minutes after study drug boluses were administered. The antiplatelet regimen was administered according to the hospital's protocol.

All patients received 300 mg of aspirin and an additional 300 mg of clopidogrel prior to the procedure. Other drugs such as Prasugrel and Ticagrelor were not administered due to their lack of availability in the concerned centers. Additional cardiovascular medications were administered according to the current guidelines. Glycoprotein IIb/IIIa inhibitors (GPI) were not administered due to cost issues and increased bleeding risks. Selection of access sites, use of aspiration and stent type were in accordance with the local standards of care and at the discretion of the operator.

Study endpoints

The primary composite endpoints were major adverse cardiac or cerebral events (MACCE) defined by all-cause death, reinfarction, ischemia-driven target vessel revascularization, or stroke, or any bleeding, as defined by the Bleeding Academic Research Consortium (BARC) definition (grades 1-5) over a period of 30 days post-PCI, and clinical follow-up after subsequent hospitalization. Severe bleeding was defined as intracranial, intraocular or retroperitoneal hemorrhage, clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL or a ≥15% absolute decrease in hematocrit. Minor bleeding was defined as clinically overt bleeding which did not meet criteria for major bleeding. Stent thrombosis was defined according to the Academic Research Consortium and was an additional safety endpoint. Myocardial infarction was defined by new significant Q waves in 2 or more contiguous

Table 2. PCI results

Characteristic	Bivalirudin (n=223)	Heparin (n=236)	P value	RR (95% CI)
Success Case	217 (97.31)	227 (96.19)	0.4988	
Failure Case	6 (2.69)	7 (2.97)	0.859	
Death Case	0 (0)	2 (0.85)	0.5036	
Noflow Case	4 (1.79)	9 (3.81)	0.192	
Slow Case	7 (3.14)	16 (6.78)	0.074	
All Cause Bleeding Case	12 (5.38)	33 (13.98)	0.002*	0.3848 (0.2039, 0.7262)
Stroke (Haemorrhagic)	2 (0.90)	7 (2.97)	0.2072	0.3024 (0.06347, 1.441)
Stent thrombosis Case	2 (0.90)	3 (1.27)	1.000	

*and the use of bold numbers means statistically significant. Abbreviations: RR: relative risk; CI: confidence interval.

Table 3. Clinical follow-up for 30 days

Characteristic	Bivalirudin (n=223)	Heparin (n=236)	P value	RR (95% CI)
All cause death	1 (0.45)	5 (2.12)	1.000	
Cardiac death	2 (0.90)	3 (1.27))	1.000	
All bleeding	9 (4.04)	25 (10.59)	0.0073*	0.3810 (0.1818, 0.7983)
Severe bleeding	1 (0.45)	13 (5.51)	0.0016*	0.0814 (0.01073, 0.6175)
MACCE	9 (4.48)	22 (9.32)	0.0241*	0.4329 (0.2037, 0.9200)
Stent thrombosis	1 (0.45)	2 (0.85)	0.9617	0.5291 (0.04829, 5.798)

*and the use of bold numbers means statistically significant. Abbreviations: RR: relative risk; CI: confidence interval; MACCE: major adverse cardiac and cerebral events.

electrocardiographic leads or by the elevation in CK-MB isoform levels, resulting in a level at least 3 times higher than the upper limit of normal values. Endpoint classifications were made by a blinded and independent clinical events committee.

Statistical analysis

The analysis was carried out rather descriptively. Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± standard deviation (SD). Comparisons between the groups of categorical data were performed by applying continuity corrected chi-squared statistic of Fisher's exact test. One way Analysis of Variance (ANOVA) was carried out for group mean comparison. Statistical significance was assumed at a value of *P*<0.05. All statistical analyses were performed with SPSS for Windows (version 20.0).

Results

A total of 459 patients were enrolled in this study from four independent centers in Jinan, Shandong Province, PRC. Two hundred and twenty three patients (48.6%) were included in

the bivalirudin arm and the remaining 236 patients (51.4%) received heparin monotherapy. Baseline characteristics and demographic data of enrolled patients are summarized in **Table 1**. Mean age in the bivalirudin and heparin arm was 5416 years and 5619 years respectively. In both treatment groups, mean age was statistically similar. One hundred and thirty seven patients (61.43%) presenting with anterior MI, 64 patients (28.70%) with inferior MI, and 22 patients (9.87%) with anterior + inferior MI were enrolled in the bivalirudin arm. One hundred and fifty six patients (66.10%) presenting with anterior MI, 56 patients (23.73%) with inferior MI, and 24 patients (10.17%) with anterior + inferior MI, were enrolled in the heparin arm. Baseline characteristics as well as treatments and procedures were well matched between the groups.

The incidence of procedural complications was low and similar between groups as demonstrated in **Table 2**, which indicates PCI results of enrolled patients assigned to the bivalirudin and heparin cohorts. Transfemoral access was used in all patients and PCI was performed with most patients receiving drug-eluting stents. Study medication adherence was high. Pro-

A. All Bleeding

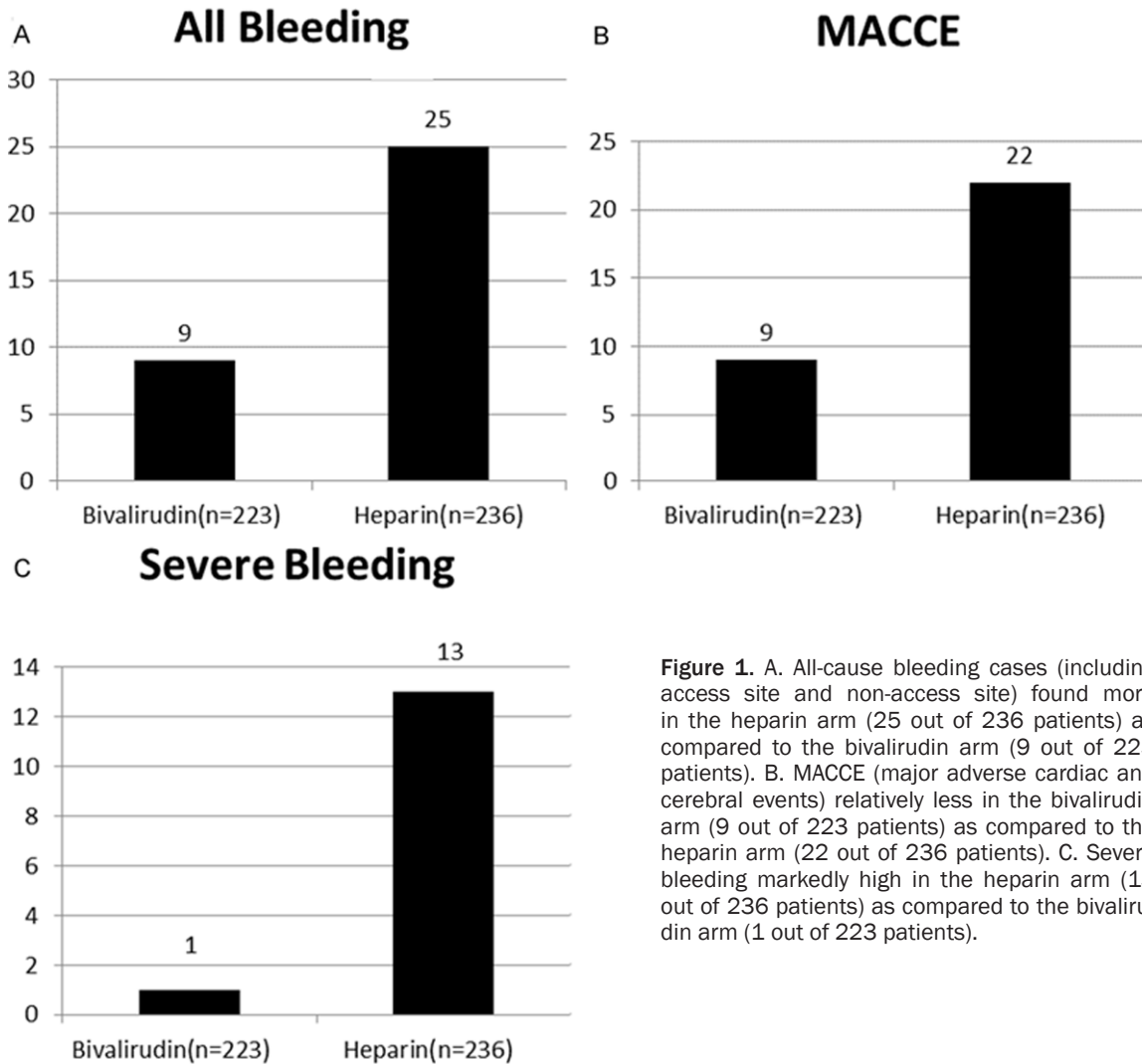## B. MACCE

C. Severe Bleeding

Figure 1. A. All-cause bleeding cases (including access site and non-access site) found more in the heparin arm (25 out of 236 patients) as compared to the bivalirudin arm (9 out of 223 patients). B. MACCE (major adverse cardiac and cerebral events) relatively less in the bivalirudin arm (9 out of 223 patients) as compared to the heparin arm (22 out of 236 patients). C. Severe bleeding markedly high in the heparin arm (13 out of 236 patients) as compared to the bivalirudin arm (1 out of 223 patients).

cedural success was found in 217 cases (97.31%) in the bivalirudin arm as opposed to 227 cases (96.19%) in the heparin monotherapy arm (*P*=0.4988). Failure was found in 6 (2.69) and 7 cases (2.97) in the bivalirudin and heparin arm, respectively (*P*=0.859). However, both these variations in results were not statistically significant. Death cases (0 *vs*. 0.85%) and no-flow (4% *vs*. 9%) cases were similar in both arms with a slightly higher percentage of slow cases in the heparin arm (7 vs. 16%) but did not reach statistical significance (*P*=0.5036, 0.192, and 0.074 respectively). The incidence of stroke (hemorrhagic) and stent thrombosis were also similar in both bivalirudin and heparin cohorts (0.9% *vs*. 2.97% and 0.9% *vs*. 1.27%, respectively). Statistical differences were also insignificant (*P*=0.2072 and P>1.00, respectively). However, there was a significant difference in the all-cause bleeding cases in

the bivalirudin arm as opposed to the heparin arm (5.38 vs. 13.98%; relative risk [RR] for bivalirudin *vs*. heparin, 0.3848; 95% CI=0.2039-0.7262; P=0.002). This difference could be attributed to the post-PCI infusion of bivalirudin, which was administered to all patients in the bivalirudin arm.

Clinical outcomes

Table 3 summarizes the 30-day clinical follow-up of all patients grouped into bivalirudin and heparin arms. As shown in **Figure 1A**, 9 patients (4.04%) treated with bivalirudin while 25 (10.59%) treated with heparin only, experienced a statistical significant difference in all bleeding events (including access and non-access sites) at the primary 30-day endpoint (relative risk [RR]=0.3810; 95% CI=0.1818-0.7983), *P*=0.0073). The rates of major adverse

cardiac or cerebral events (4.48% *vs.* 9.32%; RR=0.4329; 95% CI=0.2037-0.9200, *P*=0.0-241) and its individual components were also statistically significant between the 2 groups (**Figure 1B**). In addition, there was a statistically significant difference in the rates of severe bleeding in the bivalirudin and heparin cohorts (0.45 *vs.* 5.51%; RR=0.0814; 95% CI=0.01073-0.6175, *P*=0.0016) after 30 days (**Figure 1C**). Among patients receiving stents, no statistically significant differences were found in the 30-day rates of stent thrombosis (0.45 *vs.* 0.85, *P*=0.9617), in patients treated with bivalirudin or heparin alone.

There were also no statistically significant differences in the cardiac and all-cause deaths at 30 days in the bivalirudin and heparin arms (0.9% *vs.* 1.27%, *P*>1; and 0.45 *vs.* 2.12%, *P*>1, respectively).

Discussion

Since the inception of bivalirudin into the international market in 2001, various trials were conducted to investigate the efficacy, route of administration, primary and secondary endpoint evaluations, impact on bleeding reductions, and subsequent impact on mortality and morbidity. These trials have also demonstrated a reasonable superiority over the more conventional heparin monotherapy in reducing the consequences of major bleeding such as prolonged hospitalization, hazards of extensive blood transfusions, and death ultimately.

Our study is consistent with the findings of REPLACE-2 [16], MATRIX [22] and BRIGHT [23] trials. It shows statistically significant reductions in major bleeding (BARC 3-5) with an additional post-PCI bivalirudin infusion (*P*=0.0016). In addition, our study also demonstrates a significant reduction in all-cause bleeding (both access and non-access site) in the bivalirudin arm as compared to the heparin arm (*P*=0.0073). This finding is also consistent with the above mentioned trials and further validates the efficacy of bivalirudin as a routine antithrombotic agent superior to heparin in patients with AMI undergoing primary PCI. Furthermore, bivalirudin also exhibited superiority over heparin in reducing major coronary and cerebral events (MACCE) after 30 days of follow-up (*P*=0.0241), a finding which is inconsistent with any of the major trials in the past. This could be

attributed to lower rates of all-cause deaths, to significantly lower rates of stroke (hemorrhagic), and to the absence of apparent cases of revascularization in the bivalirudin cohort as opposed to the heparin cohort. By consequently reducing bleeding while effectively suppressing adverse ischemic events, bivalirudin improved MACCE and subsequently improved the quality of life by limiting the length of hospital stay, reducing inpatient costs, and eliminating the hazards of excessive transfusion risks.

In contrast, both the EUROMAX [27] and the HORIZONS-AMI trials [26] elicited significant reductions in bleeding and acquired thrombocytopenia but with a substantial increase in acute stent thrombosis contrary to our study which showed insignificant differences in the rates of acute stent thrombosis in both arms. The HEAT-PPCI [29] was also in sharp contrast with our study which demonstrated both significantly increased risks of acute stent thrombosis, reinfarction and MACCE with no significant reduction in bleeding. Such results could be attributed to the single center approach [30] and to the shorter duration of bivalirudin administration in the HEAT-PPCI study. However, our findings are consistent with the BRIGHT and EUROMAX trials which also showed insignificant differences in the rates of acute stent thrombosis with significant reductions in major or severe bleeding. This difference could be attributed to the higher dose of post-PCI infusion of bivalirudin (median of 3 hours). Since bivalirudin has an inherent antiplatelet activity [31], it provides a variable degree of antithrombotic protection in the early stages until the pharmacodynamics of other antiplatelet agents (e.g., clopidogrel) become active [32]. Other factors such as co-administration with heparin or the use of an immediate acting P2Y12 inhibitor such as Cangrelor could mitigate the risks of acute stent thrombosis. However, this needs to be validated in further prospective trials [33].

Much of the actions of bivalirudin could be attributed to the inhibition of fibrinogen recognition and catalytic cascades of the thrombin molecule. In addition to its direct anti-thrombin effect, bivalirudin does not require a cofactor unlike heparin, and can effectively neutralize clot-bound thrombin, and its activity is not influenced by circulating inhibitors [34]. Bivalirudin apparently does not bind to plasma proteins

and most importantly it also inhibits thrombin-mediated platelet activation in contrast to heparin, which demonstrates a platelet-activating effect [35].

Heparin requires increased doses to improve efficacy and demonstrates a greater tendency for enhanced bleeding risks. In addition, it provides incomplete and inadequate protection from periprocedural ischemic events [36]. Addition of Gp IIb/IIIa inhibitors could minimize this coherent risk of acute ischemic complications [37, 38] and subsequently reduce long-term mortality [39]. However, these agents are certainly not without limitations. Bleeding, for instance, is a major concern with these agents during initial trials with abciximab treatment demonstrating significantly increased rates of bleeding and additional transfusions to counter these adverse effects [40]. This bleeding risk could be minimized with reduction and weight-adjustment of concomitant heparin dosing but it cannot be completely eliminated [41]. Thrombocytopenia, in addition, occurs in 1 to 3% of patients with Gp IIb/IIIa inhibitor administration [37, 38] and it has been associated with increased bleeding and ischemic episodes, a need for more transfusions, and thereby prolongs hospital stay [42]. This adds to the already increasing inpatient costs along with the cost of drug acquisition, which is relatively expensive [43]. Furthermore, the 12- or 18-hour infusions of Gp IIb/IIIa inhibitors could also add to prolonged immobilization and hospitalization, which could affect outcomes and increase patient's burden.

Bleeding reduction is an important indicator of subsequent mortality as demonstrated in the pooled analysis of the ISAR-REACT, ISAR-SWEET, ISAR-SMART-2 and ISAR-REACT-2 trials, which incorporates the inclusion of periprocedural bleeding as an important composite endpoint for the assessment of outcome after PCI [44]. Our study also validates bleeding reductions, and more particularly reductions in severe bleeding as an integral part of analyzing short-term and long-term outcomes (both mortality and morbidity) in patients with AMI undergoing primary PCI.

Limitations of the study

There were several limitations to this study. First, the study population was small and it was an open-label design, thereby introducing the possibility of a potential bias. Secondly, due to the unavailability of a screening log, the generalization of the study findings cannot be accessed directly. Third, the bivalirudin used in the present study was manufactured by a different pharmaceutical company (Shenzhen Salubris Pharmaceuticals) as compared to the previous trials but it has identical molecular weight, similar anti-thrombin potency and half-life as the originator product. Fourth, in the heparin monotherapy group, we used the recommended guideline, namely a heparin dose of 100 IU/Kg [1, 2] which is higher than the dose used in previous trials but is consistent with the recent BRIGHT trial [23]. Other notable limitations include the unavailability of Prasugrel and Ticagrelor in the institutions under the present trial, the omission of Glycoprotein IIb/IIIa inhibitors (GPI) due to cost issues and patient non-compliance, and the general incorporation of all BARC bleeding points into the primary endpoint. These limitations, however, did not affect the overall study design nor did they affect the outcomes of the study.

Bivalirudin was associated with significant reductions in all-cause bleeding, severe bleeding, and major adverse coronary and cerebral events following prolonged hospitalization (30 days) which further cements its role as a novel and potent anti-thrombin drug, greatly superior to heparin. These desired effects could be attributed to the 3-hour median post-PCI bivalirudin infusion. The study also demonstrated fewer incidences of stent thrombosis as compared to heparin monotherapy contrary to the previous trials which warrants a more extensive study to evaluate the clinical efficacy of the drug and it's undermining adverse effects.

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Disclosure of conflict of interest

None.

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