Bivalirudin and Heparin Effects on Coronary Flow, Microcirculation and Recovery of Left Ventricular Systolic Function after Primary Coronary Angioplasty

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Abstract: In ST elevation myocardial infarction (STEMI) treated by primary per-coetaneous coronary intervention (PPCI), bivalirudin caused less bleeding and was as effective as combined heparin and IIb IIIa antagonist.

Aim: Compare the effects of bivalirudin and heparin on coronary flow, microcirculation and recovery of left ventricular systolic function in patients with STEMI undergoing PPCI.

Methods: Forty five patients with anterior STEMI undergoing PPCI, 30 treated with heparin and 15 with bivalirudin were compared. All patients had complete trans-thoracic Doppler echocardiographic studies and sampling of blood velocities in the left anterior descending coronary artery (LAD) early after PPCI and 5 days later.

Results: TIMI and myocardial blush grades were similar in both groups before after PPCI. Peak LAD diastolic velocities early after PPCI were higher in the bivalirudin group 42.2±14.4 compared to the heparin group 34.06±8.27 cm/sec, $p<0.03$. Peak velocities in the LAD did not change significantly on follow up in both groups. Early diastolic velocity integrals in the LAD in patients treated with bivalirudin, 12.3±4.2 were higher than in those treated with heparin, 8.91±3.21cm, $p<0.02$, and this difference between the groups was maintained on late evaluation. Left ventricular systolic function parameters were similar in both treatment groups early and late after PPCI, however only heparin was associated with increase in these parameters on discharge from the hospital.

Conclusions: Bivalirudin treatment in patients with anterior STEMI treated by PPCI was associated with higher LAD velocities and integrals compared to heparin, however only heparin increased LV systolic function after PPCI.

Keywords: Acute anterior STEMI, primary coronary angioplasty, left ventricular systolic function, Doppler echocardiography, coronary artery flow.

INTRODUCTION

The standard treatment in acute STEMI is primary percoetaneous coronary intervention (PPCI) [1-4]. PPCI requires adjunctive anti-platelet and anticoagulant treatment. In the past, unfractionated heparin, an indirect thrombin inhibitor, was the anticoagulant used in patients with STEMI treated by PPCI. However, bivalirudin, a synthetic peptide with direct reversible thrombin inhibitory activity which inhibits both circulating and thrombus bound thrombin as well as thrombin mediated platelet activation, became the adjuvant anticoagulant of choice in PPCI patients. Bivalirudin became the preferable anticoagulant after it was proved to be equivalent in efficacy but with less bleeding as compared to combined unfractionated heparin and glycoprotein IIb/IIIa inhibitor in patients with SEMI treated with PPCI [5]. Moreover, bivalirudin had a three-year survival benefit again as compared to combined unfractionated heparin and glycoprotein IIb/IIIa inhibitor in patients with SEMI treated with PPCI [6].

However in the HEAT-PPCI trial, it was found that the combined rate of major adverse coronary events was significantly lower in patients treated with unfractionated heparin compared to those treated with bivalirudin [7]. In addition, in the MATRIX trial, the rates of major adverse cardiovascular events and net adverse clinical events were not significantly lower with bivalirudin than with unfractionated heparin. The rate of the composite of urgent target-vessel revascularization, definite stent thrombosis, or net adverse clinical events was not significantly lower with a post-PCI bivalirudin infusion than without post-PCI infusion [8].

Since the above large milestone studies analyzed important clinical endpoints but without mention of echocardiographic findings, the present study was performed in order to compare the effects of bivalirudin and heparin on angiographic and Doppler-derived coronary flow and microcirculation as well as recovery of left ventricular systolic function in patients with acute STEMI undergoing PPCI.

METHODS

Forty five consecutive patients with acute ST elevation anterior myocardial infarction undergoing

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primary PCI were enrolled in the study. All fulfilled the following criteria: 1) First anterior wall STEMI. 2) PPCI within 12 hours of the onset of symptoms. 3) Routine informed consent to perform PPCI. Anterior STEMI was defined as continuous chest pain for at least 30 minutes and ST elevation of at least 2.0mm in ≥2 contiguous precordial ECG leads. Exclusion criteria included one of the following clinical or angiographic findings: Prior bypass surgery, previous anterior STEMI, significant left main artery disease, failed PPCI.

Primary PCI was performed in standard fashion. All subjects were treated with oral clopidogrel (600 mg) and aspirin (300 mg) in the emergency department. Before the Horizon trial only heparin was used and 30 consecutive patients were recruited. After the Horizon trial, only bivalirudin was used. Since coronary aspiration thrombectomy was adopted early after the initiation of bivalirudin, and since the heparin group was not treated by this method, only 15 consecutive patients treated with bivalirudin and without aspiration thrombectomy could be recruited. In the heparin subgroup, a heparin bolus 70 units/kg body weight was injected intravenously to achieve coagulation time≥250msec before the procedure, and additional doses were administered as required to keep this value and at the end of the procedure. In the bivalirudin group, 15 consecutive patients were recruited and anticoagulation was achieved with bivalirudin bolus 0.75mg/kg body weight and maintenance dose of 1.75mg/kg/hour intra-venously for 4 hours after the procedure.

Coronary angiography and PPCI were performed subsequently. Bare metal stents were deployed by high-pressure implantation techniques. Low magnification angiogram at either the right 30 º or 90 º lateral projections with prolonged cine was performed to optimize myocardial blush grade (MBG) documentation at the end of the intervention as previously described [6]. All patients were treated with clopidogrel and aspirin for 12 months after the procedure.

All patients had complete Doppler echocardiographic studies, within the first 6 hours after PPCI and 5 days after the intervention. Siemens, Acuson Sequoia echocardiographic system, California, equipped with 3.5-7MHZ transducers was used. All patients had complete Doppler echocardiographic studies, within the first 6 hours after primary PCI, 48 hours after PPCI, and 5 days after PPCI.

Chamber diameters and usual measurements were performed according to recommendations of American Society of Echocardiography. Ejection fraction of LV (LVEF) was measured from biplane apical views.

For the calculation of wall motion score index

$$LV - WMSI = \frac{\sum score\ of\ 16\ segments}{16} \quad (1)$$

assigning a value of 1 for normal LV wall motion, 2 for hypokinesis and 3 for akinesis. Using the same values of wall motion scores, LAD 9 segmental score index was calculated as:

$$LAD - WMSI = \frac{\sum score\ of\ 9\ segments}{9} \quad (2)$$

In order to obtain LAD flows, the color Doppler Nyquist limit was set at 17 cm/sec. From low parasternal short axis view, search for diastolic color flow in the anterior interventricular groove followed by clockwise rotation was performed, while form apical foreshortened two chamber views LAD diastolic flow was located in the interventricular groove and the counter clockwise rotation of the transducer was performed.

Parameters of LAD velocity patterns were averaged from 3 beats, all in sinus rhythm. Diastolic LAD deceleration Time (DDT) was measured as the time from peak diastolic velocity to the intercept of tangent of the velocity envelope with baseline.

Statistical Analysis

Statistical analysis was conducted using SPSS software version 16. All values were expressed as means and standard deviations. Categorical variables were compared by the χ^2 test. Two-tailed student's-t test was performed to compare changes in continuous parameters. $p<0.05$ was considered as statistically significant.

RESULTS

Patient Characteristics

No significant difference was found in the prevalence of atherosclerotic risk factors between the heparin and bivalirudin groups (Table **1**). In addition, the Killip class was similar in both groups (Table **1**).

Angiographic Findings

In both groups, TIMI and myocardial blush grades increased significantly after PPCI, $P<0.0001$, (Table **2**).

Table 1: Patient Characteristics

	Bivalirudin	Heparin	P(Bivalirudin vs. Heparin
N	15	30	
Male	66.7%	80%	ns
Age yrs.	58.0±11.7	59.0±12.3	ns
HTN	67%	33%	ns
HLP	80%	92%	ns
DM	20%	26.6%	ns
Current Smoker	53%	53.3%	ns
OBESITY	47%	50%	ns
FAMILY	26%	25%	ns
PVD	6.7%	6.7%	ns
Killip I	86%	75%	ns
KIlip II	13.3%	17%	ns
Killip III	0%	8%	ns
Previous CAD	13.3%	10%	ns
Pain to door(min)	133.0±85.0	143.0±103.0	ns
Door to balloon(min)	87.0±23.0	88.0±41.0	ns
Pain to balloon(min)	198.0±100.0	234.0±96.0	ns

CAD=coronary artery disease, DM= diabetes mellitus, HLP=hyperlipidemia, HTN=hypertension, PVD=peripheral vascular disease.
(Time values and age are expressed as mean± standard deviation, prevalence of all other parameters expressed in percent).

Table 2: Infarct-Related Coronary Arteriographic Flow and Myocardial Perfusion

	Pre-PPCI	Post-PPCI	P(Pre vs. Post)
TIMI- Bivalirudin (II/III)	4 (27%)	15 (100%)	<0.0001
TIMI- Heparin (II/III)	6 (20%)	29 (97%)	< 0.0001
p(Bivairudin vs. Heparin)	ns	ns	
MBG-Bivalirudin (II/III)	1 (7%)	15 (100%)	<0.0001
MBG- Heparin (II/III)	2 (7%)	29 (97%)	< 0.0001
p(Bivairudin vs. Heparin)	ns	ns	

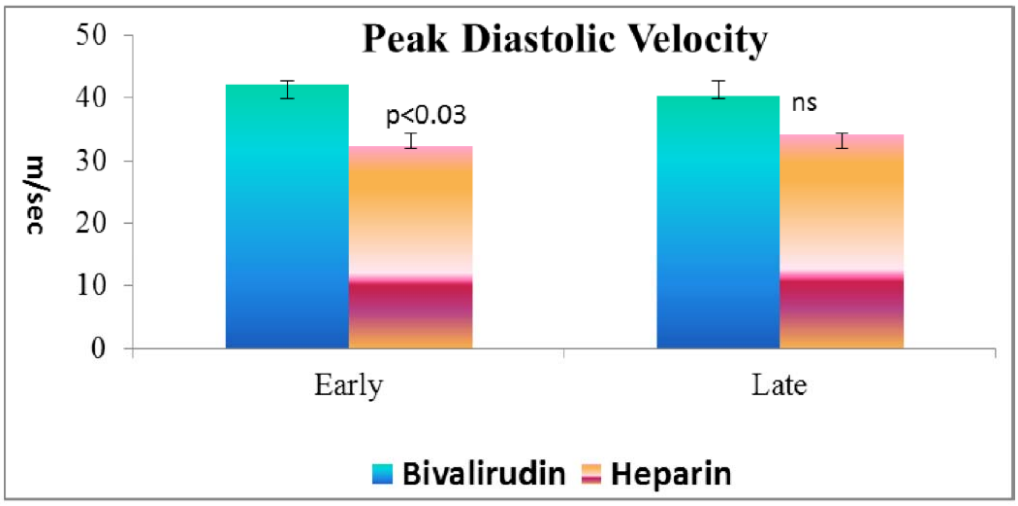
(All parameters expressed in numbers and percent).

However, TIMI and myocardial blush grades were similar in both groups, before and after PPCI, (Table **2**).

LAD Doppler-Velocity Parameters

Sampling of LAD blood velocities was possible at all occasions in all the patients. Inter and intra-observer variability of LAD velocities were 2±0.4 and 1.5±0.2 cm/sec and of time velocity integrals 0.4±0.1 and 0.3±0.1cm, and of pressure half time 10±3 and 8±3 msec.

Peak LAD diastolic velocities early after PPCI were higher in the bivalirudin group 42.2±14.4 compared to the heparin group 34.06±8.27 cm/sec, p<0.03 (Figure **1A**). Peak velocities in the LAD did not change significantly on follow up in both groups (Table **3**). Early diastolic velocity integrals in the LAD in patients treated with bivalirudin, 12.3±4.2 were higher than in those treated with heparin, 8.91±3.21 cm, p<0.02 (Figure **1B**), and this difference between the groups was maintained on late evaluation (Table **3**). On early evaluation, LAD-DDT was similar in both groups, and it increased only in the heparin group (Table **3**), and was larger in the heparin group on late evaluation (Figure **1C**). Minimal DDT was similar in both groups both on early and late evaluation (Table **3**).



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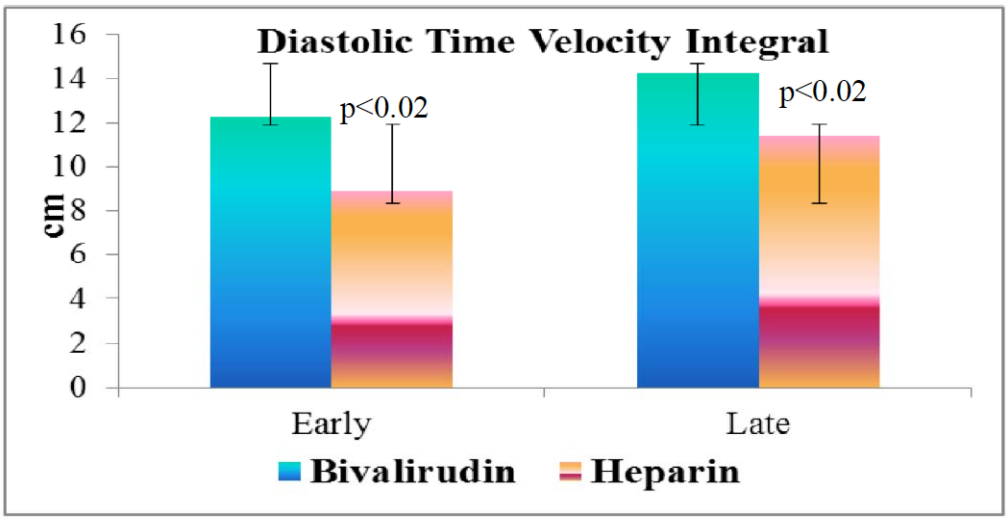

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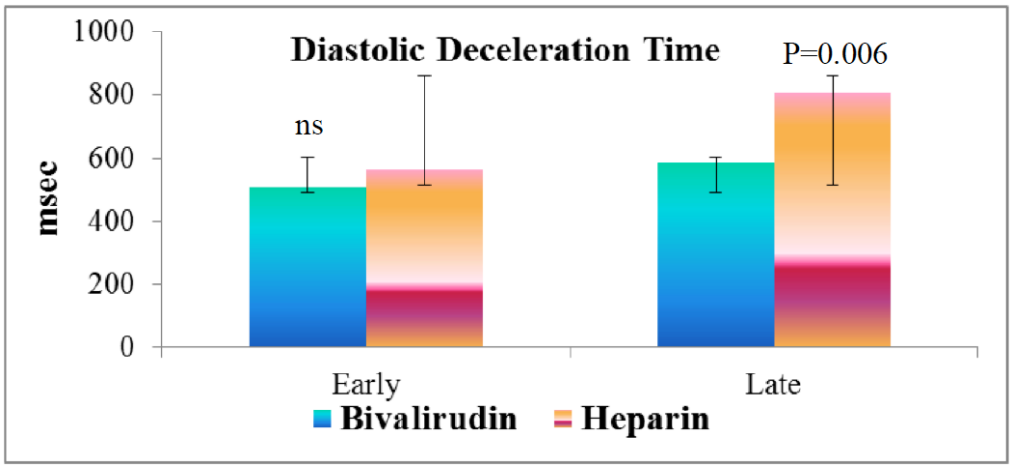

C

Figure 1: Left anterior descending coronary artery blood velocity parameters.

A- Peak diastolic velocity (cm/sec).

B- Diastolic time velocity integral (cm).

C- Diastolic deceleration time (msec).

Table 3: LAD Velocity Parameters

	Bivalirudin	Heparin	P(Bivairudin vs. Heparin)
VD Early	42.2±14.4	32.3±9.7	<0.05
VD Late	40.3±12.0	34.1±8.3	ns
p(Early vs. Late)	ns	ns	
VS Early	11.3±13.7	7.7±12.6	ns
VS Late	16.6±8.1	12.3±9.7	ns
p(Early vs. Late)	ns	ns	
TVID Early	12.3±4.2	8.9±3.2	<0.05
TVID Late	14.3±3.3	11.4±3.1	<0.05
p(Early vs. Late)	ns	<0.05	
TVIS Early	2.6±1.5	1.8±1.8	ns
TVIS Late	3.8±1.0	3.4±4.8	ns
p(Early vs. Late)	0.5	ns	
PHT Early	146.2±59.1	158.4±99.8	ns
PHT Late	191.6±57.6	238.3±105.6	ns
p(Early vs. Late)	ns	<0.05	
DDT Early	507.7±242.3	563.9±345.8	ns
DDT Late	586.0±157.0	808.9±361.3	<0.05
p(Early vs. Late)	ns	<0.05	
DDT MIN	511.5±249.0	576.3±317.3	ns

DDT: diastolic deceleration time, DDT MIN: minimal DDT, PHT: pressure half time, TVID: diastolic time velocity integral, TVIS: systolic TVI, VD: peak diastolic velocity, VS: peak systolic velocity. (All parameters are expressed as mean± standard deviation).

Table 4: Left Ventricular Systolic Function

	LVEF (%)		p*	LV-WMSI		p*	LAD-WMSI		P*
	Early	Late		Early	Late		Early	Late	
Bivalirudin	38.4 ±8.5	44.7 ±10.6	ns	1.5 ±0.3	1.4 ±0.3	ns	1.9 ±0.5	1.7 ±0.6	ns
Heparin	36.5 ±5.4	44.9 ±9.2	<0.0001	1.6 ±0.3	1.4 ±0.4	<0.05	2.0 ±0.4	1.7 ±0.5	<0.005
P**	ns	ns		ns	ns		ns	ns	

LVEF=left ventricular ejection fraction, LV-WMSI=left ventricular wall motion score index, LAD-WMSI=wall motion score index in the territory of the left anterior descending coronary artery. (All parameters are expressed as mean± standard deviation, p* = p(Early vs. Late), p**=p(Bivalirudin vs. Heparin)).

Left Ventricular Systolic Function Parameters

All three systolic function parameters; LVEF, LV-WMSI and LAD-WMSI were similar in both treatment groups early and late after PPCI, however, only in the heparin group, all the three parameters increased significant on late evaluation before discharge compared to evaluation on admission (Table **4**).

DISCUSSION

In this study, bivalirudin treatment in patients with acute anterior STEMI treated with PPCI was associated with higher LAD velocities and integrals compared to heparin. However, despite similar LV systolic function parameters between the bivalirudin and heparin groups, only heparin increased LV systolic function after PPCI.

Mechanistically, the objective of PPCI is to restore myocardial perfusion in the coronary bed distal to the occluded culprit artery. The TIMI classification [9] and myocardial blush grades [10-11] used to assess epicardial coronary artery flow and myocardial perfusion after PPCI predict outcome. However, even

with successful PPCI and the high rate of patency of the culprit artery, left ventricular functional recovery is limited and not well predicted [13, 14]. In the present study bivalirudin and heparin, as expected, increased TIMI and MBG grades significantly after PPCI, however these parameters were similar in the two treatment groups.

In addition, for the repeated physiologic evaluations of the coronary tree, Doppler sampling of coronary artery velocities by TTE became possible [15-19]. It was shown that sequential sampling of left anterior descending coronary artery (LAD) velocities in patients with acute anterior STEMI is feasible and changes during the days after primary PCI [20]. Moreover, we reported recently that the change in DDT after PPCI may change favorably or may deteriorate reflecting improvement or worsening of the function of the microcirculation [21]. Despite some differences between the bivalirudin and heparin groups in this study, minimal LAD-DDT a major determinant of recovery of left ventricular systolic function after PPCI [22], was similar in both groups.

In the HEAT-PPCI trial, which randomized 1829 STEMI patients undergoing primary percoetaneous coronary intervention found that the combined rate of major adverse coronary events was 5.7% in patients treated with unfractionated heparin and 8.7% in those treated with bivalirudin, a statistically significant difference for the study's primary efficacy endpoint [6]. The rate of major bleeding events, the study's primary safety endpoint, occurred in 3.5% of patients treated with bivalirudin and in 3.1% of those who received unfractionated heparin, a difference that was not statistically significant.

Another confirmation to the findings of our study comes from a recent meta-analysis of ten trials involving 18065 patients undergoing coronary artery angioplasty and found that bivalirudin compared to heparin did not reduce mortality, but did reduce the risk of major bleeding on the expense of high risk of stent thrombosis [23].

The present study is unique since it purely compared the effects of bivalirudin and unfractionated heparin on the mechanisms determining the outcome of patients with STEMI. In order to achieve a higher sensitivity, each phenomenon was evaluated by several independent measures. Thus, the effects on coronary flow in the infarct related artery was estimated by TIMI flow grades and non-invasive transthoracic Doppler-derived coronary artery blood velocity parameters. In addition, myocardial perfusion was assessed by myocardial blush- MBG and diastolic deceleration time of the LAD blood velocity. Left ventricular systolic function was assessed by several echocardiographic parameters, both on presentation and at discharge. Moreover, in order to perform a strict comparison between bivalirudin and unfractionated heparin, only patients having PPCI without aspiration coronary thrombectomy, and only those treated with aspirin and clopidogrel were included in this study. Since in our center the adoption of bivalirudin in the treatment of PPCI patients preceded the introduction of catheter coronary thrombus aspiration and the use of newer antiplatelet agents by a short period of time, only a rather small number of patients could be recruited [24].

In a previous mechanistic study in PPCI patients, we compared the effects unfractionated heparin alone or combined with eptifibatide [25]. Similar to the findings with bivalirudin in the present study, the eptifibatide group had higher LAD velocities compared to the unfractionated heparin group. However, contrary to the present study, left ventricular systolic function on admission and at discharge were similar between the groups. Thus it seems that unfractionated heparin therapy in the setting of PPCI is unique in achieving a significant improvement in left ventricular systolic function. However, it must be emphasized that, LV systolic function parameters were similar in both groups on admission and on discharge, but only the heparin group had a significant increase in LV systolic function. It seems that the smaller number of patients in the bivalirudin group contributed to this non-significant increase in LV function. On any case, it can be stated that bivalirudin had no superiority regarding effects on LV function.

Adoption of bivalirudin anticoagulation strategy in the setting of PPCI relied on non-inferiority in effectiveness and superiority in preventing major bleeding events. Since the trans-radial approach with its very rare bleeding complications is becoming preferable to the trans-femoral approach for PPCI [26], and since unfractionated heparin is cheaper than bivalurudin, and according to the findings of the present study it seems that treatment with unfractionated heparin in PPCI patients is valid and attractive.

LIMITATIONS

This is a single center study which included a small number of patients who were evaluated early for

recovery of left ventricular systolic function after PPCI. A multicenter study with a larger number of patients and longer period of follow up may reach more robust conclusions regarding the effects of bivalirudin and heparin in such patients.

CONCLUSIONS

In contrast to the conclusion of HORIZONS-AMI trial of superiority of bivalurudin compared to combined heparin and glycoprotein IIb/IIIa inhibitor therapy in decreasing bleeding rates and non-inferiority in outcome in patients with acute STEMI, the present study demonstrated superiority of heparin alone compared to bivalirudin in increasing left ventricular systolic function in the setting of anterior STEMI treated by primary coronary angioplasty.

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