Angiographic and clinical outcomes of bivalirudin versus heparin in patients with acute coronary syndrome undergoing percutaneous coronary intervention

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BACKGROUND: Heparin with adjunctive glycoprotein IIb/IIIa platelet receptor (GP IIb/IIIa) inhibitors has demonstrated its effectiveness in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI). Bivalirudin, a direct thrombin inhibitor, has recently been shown to be an effective alternative for patients undergoing elective PCI.

OBJECTIVES: To assess the angiographic and clinical outcomes of adjunctive pharmacological strategies in a high-risk population presenting with ACS.

METHODS: Of 891 consecutive PCI patients with ACS, 304 received bivalirudin (60.5% male, 68±11 years) and were compared with 283 who received heparin (58.7% male, 66±12 years). A 30-day major adverse cardiac event was defined as the occurrence of cardiac death, nonfatal myocardial infarction, urgent revascularization or major hemorrhage.

RESULTS: Adjunctive GP IIb/IIIa inhibitors were used in 14.1% of the bivalirudin group and in 72.4% of the heparin group ($P<0.010$). The occurrence of Thrombolysis In Myocardial Infarction (TIMI) flow less than grade 3 was lower and the achievement of angiographic success was higher in the bivalirudin group than in the heparin group (5.2% versus 8.2%, 94.7% versus 89.7%, $P=0.039$ and $P<0.010$, respectively). There was no difference between groups in the incidence of bleeding events (bivalirudin 2.0% versus heparin 3.5%, P not significant) and in 30-day major adverse cardiac events (bivalirudin 8.3% versus heparin 5.7%, $P=0.223$).

CONCLUSIONS: In the high-risk cohort undergoing PCI, bivalirudin with provisional GP IIb/IIIa inhibitors achieved better angiographic results. Although not powered to show a difference, and while acknowledging that a selection bias could have affected the data, the present study showed that bivalirudin may be as clinically effective and safe as heparin with adjunctive GP IIb/IIIa inhibitors.

Key Words: Angioplasty; Anticoagulants; Bivalirudin; Heparin; Myocardial infarction; Stents

Effets angiographiques et cliniques de la bivalirudine versus héparine chez des patients souffrant d'un syndrome coronarien aigu qui doivent subir une intervention coronarienne percutanée

HISTORIQUE : L'héparine administrée avec des inhibiteurs de la GP IIb/IIIa (inhibiteurs plaquettaires des récepteurs de la glycoprotéine IIb/IIIa) en traitement d'appoint, a prouvé son efficacité chez les patients qui présentent un syndrome coronarien aigu (SCA) et qui doivent subir une intervention coronarienne percutanée (ICP). La bivalirudine, un inhibiteur direct de la thrombine, s'est récemment révélée être une solution de rechange efficace pour les patients qui doivent subir une ICP élective.

OBJECTIF : Évaluer les résultats angiographiques et cliniques des stratégies pharmacologiques d'appoint chez une population à risque élevé présentant un SCA.

MÉTHODES : Parmi les 891 patients consécutifs devant subir une ICP pour SCA, 304 ont reçu de la bivalirudine (60,5 % de sexe masculin, âgés de 68 ± 11 ans) et ont été comparés à 283 patients qui ont reçu de l'héparine (58,7 % de sexe masculin, âgés de 66 ± 12 ans). L'incident cardiaque majeur à 30 jours était défini comme suit : mort d'origine cardiaque, infarctus du myocarde non fatal, intervention urgente de revascularisation ou hémorragie majeure.

RÉSULTATS : Des inhibiteurs de la GP IIb/IIIa en traitement d'appoint ont été utilisés chez 14,1 % des sujets du groupe sous bivalirudine et chez 72,4 % du groupe sous héparine ($p < 0,010$). La survenue de thromolyse durant l'infarctus du myocarde (TIMI) de grade inférieur à 3 a été plus faible et la réussite angiographique a été plus forte dans le groupe sous bivalirudine que dans le groupe sous héparine (5,2 %, contre 8,2 % et 94,7 %, contre 89,7 %, $p = 0,039$ et $p < 0,010$, respectivement). On n'a noté aucune différence entre les groupes quant à l'incidence des épisodes hémorragiques (bivalirudine 2,0 % versus héparine 3,5 %, p non significatif) et quant aux incidents cardiaques majeurs à 30 jours (bivalirudine 8,3 % versus héparine 5,7 %, $p = 0,223$).

CONCLUSION : Dans la cohorte à risque élevé devant subir une ICP, la bivalirudine avec inhibiteurs de la GP IIb/IIIa administrés provisoirement a donné lieu à de meilleurs résultats angiographiques. Bien qu'elle n'ait pas été dotée d'une puissance statistique suffisante pour montrer une différence et que les données aient pu subir l'effet d'un biais de sélection, cette étude a montré que, sur le plan clinique, la bivalirudine pourrait être aussi efficace et sécuritaire que l'héparine avec inhibiteurs de la GP IIb/IIIa à titre de traitement d'appoint.

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Unfractionated heparin, an indirect thrombin inhibitor, has been the antithrombotic agent of choice in percutaneous coronary intervention (PCI). However, this antithrombotic agent has been documented to have several limitations, including platelet activation and its unpredictable anticoagulation effect (1-3). These necessitated the search for additional adjunctive or alternative pharmacological therapies. Glycoprotein IIb/IIIa platelet receptor (GP IIb/IIIa) inhibitors, as adjuncts to heparin, have proven to be superior to heparin alone (4,5). However, these agents are associated with a higher frequency of bleeding (4) and are more costly (6).

Bivalirudin, a direct thrombin inhibitor, has been shown to be more effective than heparin in patients undergoing balloon angioplasty (7) and is comparable with heparin plus GP IIb/IIIa inhibitors in patients undergoing contemporary PCI (8). The Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE-2) trial (8) randomly assigned patients undergoing PCI to either heparin and GP IIb/IIIa inhibitors or bivalirudin with the provisional use of GP IIb/IIIa inhibitors. In the trial, only 22.5% of patients had undergone PCI for a recent acute coronary syndrome (ACS). Patients with ACS undergoing PCI had a higher rate of periprocedural complications than those without ACS (9-13).

Recognizing the limitations of heparin and the benefits of bivalirudin, we conceptualized the present study to assess the efficacy of bivalirudin compared with that of heparin in a cohort of patients with ACS undergoing contemporary PCI. More specifically, the study focused on the acute angiographic results and the occurrence of bleeding complications and major adverse cardiac events (MACE).

PATIENTS AND METHODS

Study population

Between October 2001 and October 2004, 1776 consecutive patients participating in the prospective Cardioquest Interventional Database underwent PCI. The database is an ongoing collection of standardized in-hospital and 30-day clinical data on all PCIs at four medical centres. During that time, 891 patients had either unstable angina or non-ST-elevation myocardial infarction (NSTEMI) as their presenting symptom. Of those, 304 received bivalirudin and 483 received heparin as the in-laboratory adjunctive antithrombotic therapy. Of the 483 patients who received heparin, 283 were included in the present study by case-matching to the bivalirudin group based on sex and the presence of diabetes mellitus. The study groups therefore consisted of 304 patients receiving bivalirudin and 283 receiving heparin.

Ten interventional operators practising in four institutions participated in the present study. All clinical and angiographic variables were defined prospectively, and data were collected using standardized methodology and were entered into a computer-based interventional cardiology database. An angiographic core laboratory blinded to the treatment groups analyzed all angiograms using predefined, standardized qualitative and quantitative angiographic elements. The prospectively collected data thus provided a realistic perspective on the management and outcomes of patients treated in community-based hospitals. The choice of agent and the use of in-laboratory GP IIb/IIIa inhibitors were at the discretion of the interventional operator. In general, if bivalirudin was used, a GP IIb/IIIa inhibitor was given only if the angiographic result was suboptimal. Bivalirudin was given as a bolus of 0.75 mg/kg and was followed by an infusion of 1.75 mg/kg for the duration of the procedure. If heparin was used alone, the

dose was 100 units/kg. If a GP IIb/IIIa inhibitor was used adjunctively to heparin, the heparin dose was reduced to 70 units/kg (to a maximum of 10,000 units). In general, no heparin infusion was given postprocedure. The mean activated clotting time (ACT) was measured at least 5 min after the bivalirudin bolus or heparin.

Angiographic core laboratory

All films compatible with the Digital Imaging and Communications in Medicine standards were blindly analyzed at Cardioquest Imaging Core Laboratories using semiautomated edge-detection computer software (QCA-CMS, Medis Medical Imaging Systems, Netherlands). Qualitative analysis was performed based on predefined, standardized elements. A total of 513 lesions were treated in the bivalirudin group and 429 were treated in the heparin group.

Definitions

'Unstable angina' was defined as the presence of angina at rest (usually lasting more than 20 min), a new onset (less than two months) of exertional angina, Canadian Cardiovascular Society (CCS) severity classification at least class III or recent acceleration of angina (less than two months) as reflected by an increase in severity of at least one CCS class to CCS class III or higher. 'NSTEMI' was defined as the presence of prolonged chest pain (more than 20 min and not relieved by rest and/or nitrates) or the presence of electrocardiographic changes in at least two leads showing ST-segment depression or new T-wave inversion with serial myocardial enzyme elevation.

'Elevated myocardial enzymes' were defined as either a troponin I or T level greater than 0.2 µg/L or an elevated total creatine phosphokinase level (greater than two times the upper limit of normal for the hospital) with a creatine kinase (muscle-brain) (CK-MB) level greater than 5% of the total creatine phosphokinase level.

'Major hemorrhage' was defined as overt bleeding in an intracranial or retroperitoneal location, resulting in a hemoglobin drop of at least 3 g/dL or the requirement of a transfusion of at least three units of blood. 'Minor hemorrhage' was defined as bleeding that is clinically important but does not qualify as major (eg, epistaxis, ecchymosis, hematoma or macroscopic hematuria). 'Hematoma' was defined as the presence of a firm mass at least 10 cm in diameter at the catheter entry site following the procedure. 'Pseudoaneurysm' was defined as the ultrasonographic presence of a periaccess site hematoma with flow communication to the access vessel.

In patients with unstable angina as their presenting symptom, 'postprocedural myocardial infarction' (MI) was defined as an enzyme level elevation (specifically, a CK-MB level rise to three times the hospital's upper limit of normal values with greater than 5% of the MB subfraction) with or without the development of new Q waves 0.03 s in width and/or at least one-third of the total QRS complex in contiguous leads. For patients undergoing PCI for the treatment of NSTEMI and in whom CK-MB levels were documented to be falling, a postprocedural MI was defined as a CK-MB level rise to above 50% of the most recent value with or without the development of new Q waves as defined above, or the development of ST-segment elevation or depression. In patients with NSTEMI as the presenting diagnosis and in whom PCI was performed before documenting peak CK-MB levels, a diagnosis of postprocedural MI was made after adjudication by physicians not involved in the PCI and was based on recurrent chest pain or new electrocardiographic changes consistent with an MI and a post-PCI CK-MB peak level greater than 50% of the previous level.

All patients had at least one set of cardiac enzyme measurements within 4 h of the procedure, and, if abnormal, serial measurements at 8 h intervals were performed until peak levels were achieved. All patients received 12-lead electrocardiograms immediately post-PCI and the following morning. 'Urgent revascularization' was defined as a procedure required within 24 h of symptom onset to minimize the occurrence of further clinical deterioration. Patients in this category were those with worsening sudden chest pain and/or congestive heart failure, acute MI, life-threatening coronary vascular anatomy, presence of an intra-aortic balloon pump, unstable angina despite intravenous nitroglycerin or those who were symptomatic at rest.

'Angiographic thrombus' before PCI was defined as a discrete mobile intraluminal filling defect with defined borders with or without associated contrast staining present on the baseline angiographic run. 'Thrombolysis In Myocardial Infarction (TIMI) flow less than grade 3' was defined as the anterograde flow in the target vessel less prompt than that of a comparable segment proximal to the target lesion as assessed on the final angiographic run. 'No reflow' was defined as the occurrence of TIMI flow less than grade 3 without obstruction in the proximal vessel any time during the course of the procedure. 'Distal embolization' was defined as the migration of a filling defect to distally occlude the target vessel or one of its major branches on the final angiographic run. 'Angiographic success' was defined as less than 50% of final diameter stenosis with TIMI grade 3 flow on the final angiographic run.

Outcome variables

The primary angiographic end point was angiographic success, and secondary angiographic end points included the occurrence of TIMI flow less than grade 3, distal embolization and no reflow. The primary clinical end point for the study was the determination of whether bivalirudin was equivalent or superior to heparin by documenting the occurrence rate of 30-day MACE (ie, nonfatal MI, urgent revascularization, major hemorrhage or cardiac death) in each study group. Secondary clinical end points included the occurrence of access site hematoma and pseudoaneurysm, minor and major bleeding and the 30-day occurrence of nonfatal MI, urgent revascularization and cardiac death.

Data collection

Patient registration forms were used to collect data and were subsequently entered into a computer-based multicentre interventional cardiology database. This data collection instrument enabled standardized reporting of selected demographic and clinical variables. Detailed data definitions were provided to ensure a standardized method of defining, evaluating and reporting specific cardiovascular events.

Statistical analysis

Data are presented as frequency distributions and simple percentages. Values of continuous variables are expressed as mean $\pm$ SD. Between-group comparisons of discrete variables were accomplished by χ^2 analysis, continuity-adjusted χ^2 analysis or a two-tailed Fisher's exact test. The comparison of means for continuous variables was conducted by an unpaired Student's *t* test. Data collected were subjected to both quantitative and qualitative analysis using the Number Cruncher Statistical Systems statistical software (NCSS, USA). A significant difference between measurements in the present study was defined as $P \leq 0.05$.

TABLE 1
Baseline clinical variables

Variable	Bivalirudin*	Heparin*	P
Number of patients	304 (100)	283 (100)	
Mean age $\pm$ SD, years	68 $\pm$ 11	66 $\pm$ 12	NS
Men	184 (60.5)	166 (58.7)	NS
Women	120 (39.5)	117 (41.3)	NS
Diabetes mellitus	101 (33.2)	98 (34.6)	NS
Hypertension	232 (76.3)	211 (74.6)	NS
Hyperlipidemia	207 (68.1)	221 (78.1)	NS
Current smoking	54 (17.8)	52 (18.4)	NS
Renal dysfunction	43 (14.1)	34 (12.0)	NS
Peripheral vascular disease	60 (19.7)	59 (20.8)	NS
Previous MI	103 (33.9)	78 (27.6)	NS
Previous CABG	81 (26.6)	91 (32.2)	NS
Previous PCI	135 (44.1)	134 (47.2)	NS
Multivessel disease	217 (71.4)	182 (64.3)	NS
NSTEMI	116 (38.2)	94 (33.2)	NS
Unstable angina	231 (76.0)	225 (79.5)	NS
Cardiogenic shock	8 (2.6)	6 (2.1)	NS
LVEF $\leq$ 30%	22 (7.2)	24 (8.5)	NS
Nonelective procedures	67 (22.0)	57 (20.1)	NS
Use of intra-aortic balloon pump	4 (1.3)	7 (2.5)	NS

*Numbers in parentheses are percentages. CABG Coronary artery bypass graft surgery; LVEF Left ventricular ejection fraction; MI Myocardial infarction; NS Not significant; NSTEMI Non-ST-elevation MI; PCI Percutaneous coronary intervention

RESULTS

Clinical characteristics and procedural variables

There were no significant differences between the patient demographic characteristics age and sex or their baseline clinical variables (Table 1). From these findings, it may be inferred that the study groups were based on the demographic and clinical characteristics of the patients who were measured.

Both groups were comparable in the distribution of NSTEMI, unstable angina, cardiogenic shock, severe left ventricular dysfunction or nonelective procedures. The mean number of stents and mean stent length per lesion were similar between the two groups (Table 2). The use of GP IIb/IIIa inhibitors by study group is shown in Table 3. The pre-PCI use of GP IIb/IIIa inhibitors was similar in both groups while its in-laboratory use was higher in the heparin group (72.4%) than in the bivalirudin group (14.1%) ($P < 0.010$). Clinical characteristics of patients in each study group receiving GP IIb/IIIa inhibitors compared with those not receiving these agents are shown in Table 4. In both groups, the presence of multivessel disease was higher in patients receiving GP IIb/IIIa inhibitors than in those not receiving these agents (86.0% versus 69.0%, $P = 0.02$). In the heparin group, the incidence of cardiogenic shock was higher in patients not receiving GP IIb/IIIa inhibitors than in those receiving them (5.1% versus 1.0%, $P = 0.03$).

The mean heparin dose given to patients in the heparin group was 6797 ± 2520 units/kg (median 6400 units/kg). The average ACT in the heparin group was lower than that in the bivalirudin group (287 ± 81 s, median 267 s versus 338 ± 54 s, median 348 s, respectively; $P < 0.01$). In the heparin group, 19.2% of patients received arterial access closure devices compared with 13.2% of those in the bivalirudin group ($P = 0.050$).

TABLE 2
Baseline angiographic and procedural variables

Variable	Bivalirudin*	Heparin*	P
Number of lesions	513 (100)	429 (100)	
Lesion location			NS
Left main artery	3 (0.6)	4 (0.9)	
LAD	138 (26.9)	139 (32.4)	
LCX	126 (24.6)	103 (24.0)	
RCA	180 (35.1)	118 (27.5)	
SVG	62 (12.1)	60 (14.0)	
Arterial graft	4 (0.8)	5 (1.2)	
Angiographic thrombus	81 (15.9)	43 (10.2)	0.012
Mean vessel size $\pm$ SD, mm	2.70 $\pm$ 0.81	2.62 $\pm$ 0.76	NS
Mean minimal lumen diameter $\pm$ SD, mm	0.64 $\pm$ 0.43	0.71 $\pm$ 0.54	NS
Mean diameter stenosis $\pm$ SD, %	74.3 $\pm$ 15.1	72.0 $\pm$ 17.3	0.031
Mean lesion length $\pm$ SD, mm	9.89 $\pm$ 5.65	9.19 $\pm$ 5.99	NS
Thrombectomy devices†	17 (3.3)	13 (3.0)	NS
Stent use	368 (71.7)	296 (69.0)	NS
Bare metal stents	210 (40.9)	237 (55.2)	<0.010
Drug-eluting stents	158 (30.8)	59 (13.7)	<0.010
Mean number of stents per lesion $\pm$ SD	0.87 $\pm$ 0.63	0.87 $\pm$ 0.69	NS
Mean stent length per lesion $\pm$ SD, mm	17.7 $\pm$ 8.2	17.2 $\pm$ 8.4	NS
Stent balloon to artery ratio	1.4 $\pm$ 0.6	1.4 $\pm$ 0.5	NS

*Numbers in parentheses are percentages; †Thrombectomy devices include AngioJet rheolytic catheter or transluminal extraction atherectomy. LAD Left anterior descending artery; LCX Left circumflex artery; NS Not significant; RCA Right coronary artery; SVG Saphenous vein graft

Baseline angiographic variables

Both groups were comparable in the distribution of treated target vessels (Table 2). The bivalirudin group lesions had more angiographic thrombi than those of the heparin group (15.9% versus 10.2%, $P=0.012$). Reference vessel size, minimal lumen diameter and lesion length were similar between the two groups. The percentage of diameter stenosis was higher in the bivalirudin group than in the heparin group (74.3 $\pm$ 15.1% versus 72.0 $\pm$ 17.3%, $P=0.031$). The use of thrombectomy devices, such as the AngioJet rheolytic catheter (Possis Medical, Inc, USA) or transluminal extraction atherectomy, was similar between both groups. Although there was no difference in stent use, more patients received drug-eluting stents in the bivalirudin group than in the heparin group (30.8% versus 13.7%, $P<0.010$).

Table 5 compares angiographic characteristics of lesions in patients receiving GP IIb/IIIa inhibitors with those of patients not receiving GP IIb/IIIa. In the bivalirudin group, lesions located in the left anterior descending artery and angiographic thrombi were more prevalent in patients receiving GP IIb/IIIa inhibitors than not (34.1% versus 25.5%, $P<0.010$, and 27.1% versus 13.6%, $P<0.010$, respectively). The minimal lumen diameter was larger and percentage of diameter stenosis smaller in lesions of patients treated with adjunctive GP IIb/IIIa inhibitors compared with those without these agents (0.80 $\pm$ 0.53 mm versus 0.60 $\pm$ 0.40 mm, $P<0.010$, and 71.4 $\pm$ 16.2% versus 76.3 $\pm$ 14.1%, $P=0.040$, respectively). In the heparin group, the number of stents and stent length per lesion were higher in those treated with adjunctive GP IIb/IIIa

TABLE 3
Glycoprotein IIb/IIIa platelet receptor (GP IIb/IIIa) inhibitor use

Variable	Bivalirudin*	Heparin*	P
Number of patients	304 (100)	283 (100)	
Pre-PCI GP IIb/IIIa inhibitor use	24 (7.9)	34 (12.0)	NS
Eptifibatide	22 (7.2)	32 (11.3)	
Abciximab	2 (0.6)	2 (0.7)	
In-lab GP IIb/IIIa inhibitor use	43 (14.1)	205 (72.4)	<0.010
Eptifibatide	26 (8.6)	109 (38.5)	
Abciximab	17 (5.6)	96 (33.9)	

*Numbers in parentheses are percentages. GP IIb/IIIa Glycoprotein IIb/IIIa platelet receptor; NS Not significant; PCI Percutaneous coronary intervention

inhibitors than in those without (0.99 $\pm$ 0.71 mm versus 0.74 $\pm$ 0.63 mm, $P<0.010$, and 18.6 $\pm$ 9.9 mm versus 15.7 $\pm$ 6.1 mm, $P=0.016$, respectively).

Final angiographic results (Table 6)

The incidence of TIMI flow less than grade 3 was significantly lower in the bivalirudin group (4.5%) than in the heparin group (7.9%) ($P=0.039$). The occurrence of no reflow and distal embolization was similar in both groups. Although the final mean lumen diameter of lesions in both groups was similar, the final percentage of diameter stenosis was significantly lower in the bivalirudin group (18.0 $\pm$ 16.9%) than in the heparin group (23.3 $\pm$ 21.9%) ($P<0.010$). Angiographic success was higher in the bivalirudin group (94.7%) than in the heparin group (89.7%) ($P<0.010$).

In-hospital and 30-day follow-up events (Tables 7 and 8)

There were six minor and major bleeding events (2%) in the bivalirudin group and 10 such events (3.5%) in the heparin group. A between-group comparison of the individual bleeding events for the two groups did not achieve statistical significance ($P=0.246$). By hospital discharge, there were four pseudoaneurysms (1.3%) and nine hematomas (3.0%) in the bivalirudin group compared with three (1.1%) and six (2.1%), of these events, respectively, in the heparin group. These differences did not reach statistical significance ($P=0.6775$ and $P=0.519$, respectively).

By 30 days, eight patients (four from each group) were lost to follow-up, resulting in follow-up data available for 300 bivalirudin and 279 heparin patients. The occurrence rate of 30-day MACE was 5.7% in the heparin group and 8.3% in the bivalirudin group; this difference did not achieve statistical significance ($P=0.223$). By 30 days, there were five cardiac deaths (1.7%) in the bivalirudin group and one (0.4%) in the heparin group; this difference did not reach statistical significance ($P=0.120$). There were 13 nonfatal MIs (4.3%) and five urgent revascularizations (1.7%) in the bivalirudin group compared with 10 (3.6%) and three (1.1%) of these events, respectively, in the heparin group ($P=0.644$ and $P=0.542$, respectively). All events occurred before discharge.

DISCUSSION

The present study compares the use of heparin with that of bivalirudin in patients presenting with ACS undergoing contemporary PCI in community-based hospitals. It represents an effort to critically assess the efficacy of bivalirudin in patients

TABLE 4
Clinical determinants of the use of glycoprotein IIb/IIIa platelet receptor (GP IIb/IIIa) inhibitors in the bivalirudin and heparin groups

Variable	Bivalirudin*			Heparin*		
	GP IIb/IIIa inhibitors	No GP IIb/IIIa inhibitors	P	GP IIb/IIIa inhibitors	No GP IIb/IIIa inhibitors	P
Number of patients	43 (100)	261 (100)		205 (100)	78 (100)	
Mean age $\pm$ SD, years	66 $\pm$ 11	68 $\pm$ 11	NS	66 $\pm$ 11	67 $\pm$ 12	NS
Men	26 (60.5)	158 (60.5)	NS	126 (61.5)	40 (51.3)	NS
Women	17 (39.5)	103 (39.5)	NS	79 (38.5)	38 (48.7)	NS
Diabetes mellitus	9 (20.9)	92 (35.2)	NS	72 (35.1)	26 (33.3)	NS
Hypertension	32 (74.4)	200 (76.6)	NS	154 (75.1)	57 (73.1)	NS
Hyperlipidemia	32 (74.4)	175 (67.0)	NS	160 (78.0)	61 (78.2)	NS
Current smoking	6 (14.0)	48 (18.4)	NS	41 (20.0)	11 (14.1)	NS
Renal dysfunction	5 (11.6)	38 (14.6)	NS	28 (13.7)	6 (7.7)	0.057
Peripheral vascular disease	4 (9.3)	56 (21.5)	NS	43 (21.0)	16 (20.5)	NS
Previous MI	12 (27.9)	91 (34.9)	NS	60 (29.3)	18 (23.1)	NS
Previous CABG	12 (27.9)	69 (26.4)	NS	71 (34.6)	20 (25.6)	NS
Previous PCI	17 (39.5)	118 (45.4)	NS	94 (45.9)	40 (51.3)	NS
Multivessel disease	37 (86.0)	180 (69.0)	0.02	140 (68.3)	42 (53.8)	0.02
NSTEMI	8 (18.6)	65 (24.9)	NS	42 (20.5)	16 (20.5)	NS
Unstable angina	35 (81.4)	196 (75.1)	NS	163 (79.5)	62 (79.5)	NS
Cardiogenic shock	1 (2.3)	7 (2.7)	NS	2 (1.0)	4 (5.1)	0.03
LVEF $\leq$ 30%	1 (2.3)	21 (8.0)	NS	19 (9.3)	5 (6.4)	NS
Nonelective procedures	11 (25.6)	53 (20.3)	NS	47 (22.9)	10 (12.8)	0.068
Use of intra-aortic balloon pump	1 (2.3)	3 (1.1)	NS	6 (2.9)	1 (1.3)	NS

*Numbers in parentheses are percentages. CABG Coronary artery bypass graft surgery; LVEF Left ventricular ejection fraction; MI Myocardial infarction; NS Not significant; NSTEMI Non-ST elevation MI; PCI Percutaneous coronary intervention

TABLE 5
Baseline angiographic determinants of the use of glycoprotein IIb/IIIa platelet receptor (GP IIb/IIIa) inhibitors in the bivalirudin and heparin groups

Variable	Bivalirudin*			Heparin*		
	GP IIb/IIIa inhibitors	No GP IIb/IIIa inhibitors	P	GP IIb/IIIa inhibitors	No GP IIb/IIIa inhibitors	P
Number of lesions	85 (100)	428 (100)		326 (100)	103 (100)	
Lesion location			<0.010			NS
Left main artery	2 (2.4)	1 (0.2)		4 (1.2)	0 (0)	
LAD	29 (34.1)	109 (25.5)		110 (33.7)	29 (28.2)	
LCX	12 (14.1)	114 (26.6)		79 (24.2)	24 (23.3)	
RCA	29 (34.1)	151 (35.3)		79 (24.2)	39 (37.9)	
SVG	13 (15.3)	49 (11.4)		49 (15.0)	11 (10.7)	
Arterial graft	0 (0)	4 (0.9)		5 (1.7)	0 (0)	
Angiographic thrombus	23 (27.1)	58 (13.6)	<0.010	35 (10.9)	8 (7.8)	NS
Mean vessel size $\pm$ SD, mm	2.82 $\pm$ 0.89	2.75 $\pm$ 0.75	NS	2.73 $\pm$ 0.83	2.43 $\pm$ 0.59	<0.010
Mean minimal lumen diameter $\pm$ SD, mm	0.80 $\pm$ 0.53	0.60 $\pm$ 0.40	<0.010	0.70 $\pm$ 0.54	0.67 $\pm$ 0.49	NS
Mean diameter stenosis $\pm$ SD, %	71.4 $\pm$ 16.2	76.3 $\pm$ 14.1	0.040	73.2 $\pm$ 17.2	72.2 $\pm$ 18.5	NS
Mean lesion length $\pm$ SD, mm	10.5 $\pm$ 5.9	10.2 $\pm$ 6.0	NS	9.43 $\pm$ 6.68	9.38 $\pm$ 5.66	NS
Mean number of stents per lesion $\pm$ SD	1.0 $\pm$ 0.8	0.9 $\pm$ 0.6	NS	0.99 $\pm$ 0.71	0.74 $\pm$ 0.63	<0.010
Mean stent length per lesion $\pm$ SD, mm	17.7 $\pm$ 11.7	17.8 $\pm$ 8.3	NS	18.6 $\pm$ 9.9	15.7 $\pm$ 6.1	0.016

*Numbers in parentheses are percentages. LAD Left anterior descending artery; LCX Left circumflex artery; NS Not significant; RCA Right coronary artery; SVG Saphenous vein graft

with ACS outside the constraints posed by a randomized clinical trial. To our knowledge, it is the first study that compares the angiographic outcomes of the two strategies as objectively assessed by a core laboratory.

In the present study, the baseline clinical characteristics of both groups were well-matched, specifically with respect to variables associated with increased periprocedural complications

(eg, cardiogenic shock, severe left ventricular dysfunction and nonelective procedures). There was, however, a significantly higher use of intraprocedural GP IIb/IIIa inhibitors in the heparin group than in the bivalirudin group, reflecting the results of recently completed trials (4,5) that showed the benefits of this combination of antithrombin agents in patients with ACS. On the other hand, these agents were only used

TABLE 6
Final angiographic variables

Variable	Bivalirudin*	Heparin*	P
Number of lesions	513 (100)	429 (100)	
Mean minimal lumen diameter $\pm$ SD, mm	2.34 $\pm$ 0.75	2.24 $\pm$ 0.80	NS
Mean diameter stenosis $\pm$ SD, %	18.0 $\pm$ 16.9	23.3 $\pm$ 21.9	<0.010
TIMI flow grade <3	23 (4.5)	34 (7.9)	0.039
No reflow	5 (1.0)	4 (1.0)	NS
Distal embolization	2 (0.4)	0	NS
Angiographic success	486 (94.7)	385 (89.7)	<0.010

*Numbers in parentheses are percentages. NS Not significant; TIMI Thrombolysis In Myocardial Infarction

adjunctively to bivalirudin if the operator felt that more aggressive antiplatelet therapy was warranted. Indeed, the presence of multivessel disease, angiographic thrombi and lesions in the left anterior descending artery was associated with greater GP IIb/IIIa inhibitor use adjunctive to bivalirudin.

The 30-day clinical outcomes of the two strategies in our study are in agreement with those of the REPLACE-2 trial. However, only 22% of the randomly assigned patients in REPLACE-2 had unstable angina or NSTEMI, whereas the present study specifically addressed the high-risk group of patients with ACS, thus expanding the effectiveness of bivalirudin to this population.

With the exception of angiographic thrombi and percentage of diameter stenosis, baseline angiographic variables were similar between the two groups. The present study showed that patients undergoing PCI who had lesions and were in the bivalirudin group had better TIMI flow rates – translating into higher angiographic success rates – than those in the heparin group. These findings are even more significant considering the higher prevalence of angiographic thrombi, a factor associated with higher complication rates (14), in patients with lesions treated with bivalirudin (15.9%) than in those treated with heparin (10.2%, $P=0.012$). It is unclear why there was a lower final percentage of diameter stenosis in the bivalirudin group because such a finding is unlikely to be drug-related.

The clinical and angiographic findings in our study suggest that bivalirudin, by virtue of its predictable direct thrombin inhibition (15-17) without platelet activation (18), may confer an advantage over heparin even when combined with a GP IIb/IIIa inhibitor. Although heparin is considered the 'gold standard' in patients undergoing PCI, it has several limitations that may adversely affect patient outcomes, including its ability to only inhibit fluid-phase thrombin and its neutralizing effect by circulating intrinsic inhibitors (eg, platelet factor 4) (3,16). Its platelet activation ability (3,17) is an additional deterrent.

Unlike previous trials, the present study failed to demonstrate that the use of bivalirudin resulted in a significant reduction of bleeding events. This is possibly due to the fact that the overall bleeding rate in the present study (4%) was low compared with what was observed in the REPLACE-2 trial (15%). On the other hand, the bleeding rates we observed are similar to those previously seen in GP IIb/IIIa inhibitor trials, such as Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT [19]) and Evaluation of PTCA to Improve Long-Term Outcome by c7E3 Glycoprotein IIb/IIIa Receptor Blockade (EPILOG [20]), possibly relating to the fact that the GP IIb/IIIa inhibitor adjunctive

TABLE 7
Hemorrhagic complications

Variable	Bivalirudin*	Heparin*	P
Number of patients	304 (100)	283 (100)	
Pseudoaneurysm	4 (1.3)	3 (1.1)	NS
Hematoma	9 (3.0)	6 (2.1)	NS
Minor hemorrhage	5 (1.6)	8 (2.8)	NS
Major hemorrhage	1 (0.3)	2 (0.7)	NS
Any hemorrhage	6 (2.0)	10 (3.5)	NS

*Numbers in parentheses are percentages. NS Not significant

TABLE 8
Thirty-day clinical outcomes*

Variable	Bivalirudin†	Heparin†	P
Number of patients	300 (100)	279 (100)	
Cardiac death	5 (1.7)	1 (0.4)	NS
Nonfatal myocardial infarction	13 (4.3)	10 (3.6)	NS
Urgent revascularization	5 (1.7)	3 (1.1)	NS
Major adverse cardiac events‡	25 (8.3)	16 (5.7)	NS

*Eight patients were lost to follow-up (four from each of the bivalirudin and heparin groups); †Numbers in parentheses are percentages; ‡Major adverse cardiac events include cardiac death, nonfatal myocardial infarction, urgent revascularization or major hemorrhage. NS Not significant

heparin-dosing strategy of 70 units/kg we used, which resulted in a median ACT of 267 s, was similar to what was reported in these trials. In the heparin/GP IIb/IIIa inhibitor arm of REPLACE-2, the median ACT was 317 s, possibly explaining the higher bleeding rates in that group of patients.

One of the advantages of bivalirudin use over the heparin/GP IIb/IIIa inhibitor combination is cost savings. Cohen et al (21) found that in 4651 American patients in the REPLACE-2 trial, there was a per-patient savings of US\$400 and US\$375 in in-hospital and 30-day costs, respectively, favouring bivalirudin over a strategy of heparin/GP IIb/IIIa inhibitors. Eighty per cent of this cost savings was related to anticoagulant therapy, and 20% to outcomes and complications costs. Although our study was not designed to assess the economic impact of the two strategies in patients with ACS, we can note that compared with Cohen et al's study, 72% of our patients receiving heparin (versus 100% in Cohen et al's study) also received a GP IIb/IIIa inhibitor and 14% of those receiving bivalirudin (versus 7.7%) also received a GP IIb/IIIa inhibitor. Therefore, this may reduce the anticoagulant cost reduction benefit of using bivalirudin.

Study limitations

The present study had several important limitations that must be addressed. First, although it shows no difference in the primary end points, the number of study subjects should be larger to confirm the findings of the study.

Second, comparing outcomes of 'matched groups' on the basis of selected key preprocedural demographic and clinical characteristics using univariate analysis is rarely successful. Multivariate analyses are generally required to adjust for differences that may not necessarily be obvious to the investigator. A propensity analysis with a sufficient number of patients may have been the preferred choice in determining the homogeneity of the groups.

Third, the findings of the present study cannot be applied to the entire range of patients undergoing PCI because selectivity was a factor in the study. The data may have been influenced by a bias in the selection of heparin or bivalirudin based on the interventional cardiologist's experience with either agent. Operator discretion, not random assignment, dictated the use of the antithrombin agent administered during the course of the study.

Finally, because of the small number of outcome events that occurred, it is difficult to determine how much of the observed changes in MACE or ischemic outcomes were the direct result of the antithrombin agent used.

CONCLUSIONS

Although the present study was not powered to show a difference in events, it showed that the use of bivalirudin with provisional GP IIb/IIIa inhibitors may be equivalent to a heparin/GP IIb/IIIa inhibitor strategy in patients with ACS undergoing PCI. Bivalirudin results in better angiographic results, and represents a new and attractive alternative to heparin, which, as demonstrated in the present study, often requires the use of adjunctive GP IIb/IIIa inhibitors.

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