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Original Article

Comparison of anti-thrombotic strategies using Bivalirudin, Heparin plus Glycoprotein IIb/IIIa inhibitors and Unfractionated Heparin Monotherapy for patients undergoing percutaneous coronary intervention – A single centre observational study☆

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ABSTRACT

Aims: The study was planned to compare Anti-thrombotic strategies for patients undergoing PCI in a real world population with an emphasis on occurrence of major bleeding, composite ischemic end points and economic outcomes.
Methods: The present study is a single center, prospective, observational study in consecutive patients undergoing PCI at Fortis Escorts Heart Institute (FEHI) and describes Authors' experience with three different Anti-Thrombotic Strategies in a real world population. Patients were consecutively enrolled in the study and the choice of Anti-thrombotic strategy was left to individual operator(s) based on their own clinical judgment and patient's affordability. No specific inclusion/exclusion criteria were specified on the choice of Anti-Thrombotic Strategy.
Results: A total 1453 patients were consecutively enrolled into the study and were followed telephonically after 30 days. 252 patients were treated with Bivalirudin (Angiomax) during PCI (17.3%), 430 (29.6%) patients were treated with Heparin plus GPI & remaining 771 (53.1%) were treated with Heparin monotherapy. Incidence of major bleeding was lowest in patients treated with Bivalirudin (1.59%) when compared to Heparin plus GPI (3.49%) and Heparin monotherapy (5.97%), $p = 0.005$ Bivalirudin vs. Heparin Monotherapy, and $p = 0.145$, Bivalirudin vs. Heparin + GPI. No bleeding was observed in STEMI patients treated with

☆ Read the Editorial to this manuscript: BRIGHT HORIZONS for Bivalirudin? EUROMAXimizing benefits of bleeding risk but catching a MATRIX of HEAT for stent thrombosis.

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Bivalirudin compared to 7.4% in patients treated with GPI and 14.3% in patients treated with UFH. Similarly non-access site bleeding was lowest in patients treated with Bivalirudin. Only 4 patients (1.6%) treated with Bivalirudin required Blood transfusion compared to 25 in Heparin plus GPI (5.8%) and 38 (5%) in Heparin Monotherapy arm. In Composite Ischemic end-points, no "All-cause Mortality" was observed in Bivalirudin group compared to 2.8% in Heparin plus GPI. Early stent thrombosis was seen in 1 patient with Heparin plus GPI and none with Heparin monotherapy and Bivalirudin group. None of the patients underwent TLR (target lesion revascularization) and TVR (target vessel revascularization) within 30 days post procedure other than one early stent thrombosis reported with Heparin plus GPI. Cost of blood product transfusion was lower with Bivalirudin as compared to Heparin plus GP IIb/IIIa arm ($p = 0.01$) and with Heparin alone ($p = 0.001$). Due to lower complications including blood transfusions and reduced hospital stay in Bivalirudin group, these benefits outweigh the incremental cost due to higher acquisition cost of the drug.

Conclusion: Bivalirudin use during PCI is associated with a distinct advantage of having lower access site and non-access site bleeding without compromising on the efficacy. We observed a reduction in blood transfusions, hospital stay and mortality for patients treated with Bivalirudin compared with Heparin plus GPI or Heparin Monotherapy. Bivalirudin can be safely adopted into our Institutional protocol for the treatment of high risk PCI such as STEMI, ACS, and Complex elective PCI.

1. Introduction

Anti-coagulation during PCI is very important to the outcomes. Heparin, Heparin plus GPI and Bivalirudin are the currently used Anti-coagulation strategies. Randomized clinical trials and various meta-analyses have shown that Direct Thrombin Inhibitor Bivalirudin significantly reduces bleeding-related complications in patients undergoing PCI.[1–5] Based on this evidence, Bivalirudin has received a class I recommendation as anticoagulant for PCI.[6,7] From an Indian perspective, there is an inherent dearth of data in ACS patients undergoing invasive therapy with different anti-thrombotic management outcomes. There have been no published studies in India that have been conducted to understand the different anti-thrombotic managements outcomes in terms of frequent hemorrhagic complications and the cost involved in such management. Data from various registries have shown that ACS patients in India tend to be young, from low socio-economic groups, have a higher rate of STEMI than patients in developed countries. They receive delayed medical attention and proven therapies less often and have higher 30-day mortality than high socio-economic groups.[8] Hence, evidence concerning the benefits of the many potential anti-thrombotic agents in terms of hemorrhagic complications and the cost incurred for such managements used in a real-life setting is lacking. We chose to study the impact of different Anti-thrombin strategies at a high volume Tertiary Care center in a real world population to generate evidence and future directions.

2. Methods

The present study is a single center, prospective, observational study in consecutive patients undergoing PCI at Fortis Escorts Heart Institute (FEHI) and captures authors' experience with three different Anti-Thrombotic Strategies in an all comer patient population. The Institutional Ethics Committee (IEC) approval was obtained prior to initiation of the study. 1450 patients were consecutively enrolled between June 2013–Dec 2013 and the choice of Anti-thrombotic strategy was left to individual operator(s) based on their own clinical judgment and patient's affordability. No specific inclusion/exclusion criteria were specified on the choice of Anti-Thrombotic Strategy.

3. Study protocol

Patients who underwent PCI were divided into 3 cohorts depending on the Anti-thrombotic treatment. First group received Bivalirudin as intravenous bolus of 0.75 mg/kg, followed by an infusion of 1.75 mg/kg/hour. Our institutional protocol requires us to continue the Bivalirudin infusion post procedure at a minimum of running the entire bag out. Second group was administered Heparin plus a Glycoprotein IIb/IIIa Inhibitor (GPI) as per the standard hospital guidelines. Third group was administered Unfractionated Heparin Monotherapy (UFH) as an intravenous bolus of 60 IU/kilogram of body weight, with subsequent boluses targeted to an activated clotting time (ACT) of >300 s. The Anti-platelet regimen was given according to the hospital protocol.

Patients more than 18 years old were enrolled into the study based on the following eligibility criteria:

3.1. *Inclusion criteria*

The clinical classification of patients was done according to recent ACC/AHA Guidelines.[9]

1) STEMI >20 min and <12 h in duration
   a) ST-segment elevation of ≥1 mm in ≥2 contiguous leads; or
   b) Presumably new left bundle branch block (LBBB); or
   c) True posterior myocardial infarction (MI) with ST depression of ≥1 mm in ≥2 contiguous anterior leads.
2) NSTEMI/Unstable angina.
3) Chronic stable angina.
4) Written informed consent.

3.2. *Exclusion criteria*

1) Contraindication to any of the study medications.
2) Prior administration of thrombolytic therapy, Bivalirudin, GPI, LMWH or Fondaparinux (Factor Xa Inhibitor) for the present admission (prior UFH allowed).
3) Current use of Coumadin.
4) History of bleeding diathesis or known coagulopathy (including HIT)
5) History of Intracerebral Mass, Aneurysm, Arteriovenous Malformation (AVM), or hemorrhagic stroke; stroke or transient ischemic attacks (TIA) within 6 months or any permanent neurologic deficit; gastrointestinal (GI) or genitourinary (GU) bleed within 2 months, or major surgery within 6 weeks; recent or known platelet count <100,000 cells/mm^3 or hgb <10 g/dL.

Data from patients from all three arms was collected prospectively during hospital stay and then through 30 day telephonic follow up. Following analysis was done-

1) Major Bleeding (not related to CABG) was defined as:
   - Any intracranial bleeding (excluding microhemorrhages <10 mm evident only on gradient-echo MRI)
   - Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL or a ≥15% absolute decrease in hematocrit
   - Fatal bleeding (bleeding that directly results in death within 7 d)
2) Composite end point, defined as all cause death, myocardial infarction, unplanned revascularization for ischemia within 30 days.
3) Cost Analysis – in the form of days in hospitalization after PCI. Special treatment required in the form of surgical interventions and blood transfusions were also considered for cost analysis.

Stent thrombosis was defined according to the Academic Research Consortium.[10] Myocardial re-infarction was defined to have occurred, if 2 of the following 5 criteria were present:

i. chest pain lasting longer than 30 min;
ii. substantial changes on ECG that were typical of acute myocardial infarction (an ST-segment elevation of 0.1 mV in at least 2 adjacent ECG leads or the new occurrence of a complete left bundle-branch block);
iii. a substantial increase in the level of CK-MB isoform (at least 3 times the upper normal value);
iv. new, clinically significant Q waves; and
v. chest pain leading to angiography up to 6 h after the onset of the pain, with angiographic evidence of a totally occluded vessel.

4. Statistical analysis

Descriptive analysis was carried out. Categorical variables were presented in number and percentage (%) and continuous variables presented as mean ± standard deviation (SD). Between groups, comparison was performed by applying continuity corrected chi-squared statistic of Fisher's exact test for categorical data. Analysis of variance (ANOVA) was carried out for comparison of group mean. A Two-proportion Z test was used to analyze the cost effectiveness. Statistical significance was assumed at a value of $p = 0.05$. All statistical analyses was performed with SPSS for windows (version 13.0).

5. Results

A total of 1453 patients were enrolled into this study. 17.3% were in Bivalirudin arm, 29.6% received Heparin plus GPI and 53.1% were administered Heparin Monotherapy (Table 1).

Mean age in Bivalirudin, Heparin plus GPI & Heparin arm were 61.1 ± 11.02 years, 59.5 ± 10.0 and 61.3 ± 10.9 years, respectively. In all the three treatment groups, mean age was statistically similar (Bivalirudin and Heparin plus GPI; $p = 0.37$, Bivalirudin and Heparin; $p = 0.669$, Heparin plus GPI and Heparin; $p = 0.85$).

Table 2 shows demography and baseline clinical charcteristics of the enrolled patients. The number of males was significantly higher in GPI arm (97.2%). There were 80.4% males in Heparin arm and 77.8% in Bivalirudin arm ($p = 0.342$). Bivalirudin arm had more diabetic patients (46.6%) than Heparin plus GPI (12.09%; $p = 0.0001$) but were comparable between Bivalirudin and Heparin (41.1%, $p = 0.07$). There were less hypertensive patients in GPI cohort, but it did not reach statistical significance ($p = 0.524$). Table 3 summarizes the comorbid conditions for these patients. Clopidogrel was the most common anti-platelet used. Newer anti-platelet drugs Prasugrel & Ticagrelor were used more in Bivalirudin 37.7% (p value = 0.0001) and 15.8% (p value = 0.0001), respectively

Table 1 – Treatment arms and patient distribution.

Group	Treatment protocol	No. of patients	Percentage
Bivalirudin	Patients who were being managed with Bivalirudin	252	17.3%
Heparin+ GPI	Patients who were being managed with Heparin plus GPI, either bolus or infusion	430	29.6%
Heparin	Patients who were being managed with Heparin alone	771	53.1%

Table 2 – Demographics and baseline clinical characteristics.

Variable	Bivalirudin ($n = 252$)	Heparin+GPI($n = 430$)	Heparin ($n = 771$)	Statistical significance
Mean age ± SD in years	61.1 ± 11.02	59.5 ± 10.0	61.3 ± 10.9	–
Male	196 (77.78%)	418 (97.21%)	621 (80.54%)	$\chi^2 = 72.6$ $p = 0.0001$ (S)
Female	56 (22.22%)	12 (2.79)	150 (19.46%)	
History of Diabetes Mellitus	120 (47.6%)	52 (12.09%)	317 (41.11%)	$\chi^2 = 130.7$ $p < 0.0001$ (S)
History of Hypertension	152 (60.31%)	272 (61.16%)	462 (59.9%)	$\chi^2 = 1.34$ $p = 0.510$ (NS)
ACS	242 (94%)	422 (98.1%)	699 (90.7%)	$\chi^2 = 1.8$; $p = 0.405$ (NS)
Clopidogrel	119 (47.2%)	350 (81.4%)	656 (85.1%)	$\chi^2 = 161.$; $p = 0.000$(S)
Prasugrel	95 (37.7%)	74 (17.2%)	96 (12.4%)	$\chi^2 = 816$; $p = 0.0001$ (S)
Ticagrelor	38 (15.1.%)	6 (1.4%)	19 (2.5%)	$\chi^2 = 85.6.$; $p = 0.0001$ (S)

Table 3 – Co-morbid conditions.

Arm	Diabetes	Non-diabetics	HTN	Non-HTN	Total
Bivalirudin	120 (47.6%)	132	152 (60.31%)	100	252
Heparin + GPI	52 (12.09%)	378	272 (61.6%)	158	430
Heparin	317 (41.11%)	454	462 (59.9)	309	771

HTN: Hypertension.

(Table 4). Majority of patients in all the arms undergoing PCI were having ACS (93.8%) with Unstable Angina (UA) being the leading indication for PCI (Fig. 1). Stable angina patients undergoing PCI were more in Heparin arm (9.3%) than other 2 groups (Table 5). STEMI patients were more in Bivalirudin treatment arm and Heparin plus GPI group when compared with Heparin alone. STEMI patients were similar in Bivalirudin (19.4%) as compared to Heparin plus GPI (21.9%; $p = 0.454$).

Major Bleeding was 1.59% in Bivalirudin arm; 3.49% in Heparin plus GPI and 5.97% in Heparin arm with statistically significant bleeding with Heparin versus Bivalirudin ($p = 0.005$). There was no statistically significant difference in bleeding between Bivalirudin and Heparin plus GPI ($p = 0.145$).

There was no bleeding observed in STEMI patients treated with Bivalirudin compared to 7.4% in STEMI patients treated with GPI and 14.3% in STEMI patients treated with UFH. Table 6 summarizes bleeding incidences in various groups.

Composite End Point, (all cause death, myocardial infarction unplanned revascularization for ischemia within 30 days).

30 Day Mortality: All-cause mortality within 30 days was 2.8% in Heparin plus GPI cohort and none in Heparin and Bivalirudin alone treatment arm.

Stent Thrombosis: Early definite stent thrombosis was seen in 1 patient who was on Heparin plus GPI. There was no case reported in Heparin group and Bivalirudin alone.

TLR and TVR within 30 days: None of the patients underwent TLR & TVR within 30 days post procedure other than one early stent thrombosis reported with Heparin plus GPI.

Unplanned Revascularization: No Unplanned Revascularization was observed in any group.

Cost Analysis: Mean Cost of blood product transfusions was INR 111.11 in Bivalirudin treated group, INR 308.98 with Heparin plus GPI and INR 373.54 with Heparin alone. Cost of blood product transfusion was lower with Bivalirudin as compared to Heparin plus GP IIb/IIIa arm ($p = 0.01$) and with Heparin alone ($p = 0.001$). After adding the acquisition cost of anti-thrombotic therapy and stay in hospital, the treatment cost increased to INR 16, 693 with Bivalirudin alone, INR 10,440 with Heparin plus GPI and INR 1307 with Heparin alone (Table 7). The benefits on account of lesser blood transfusion and reduced hospital stay still outweigh the incremental costs of drug acquisition.

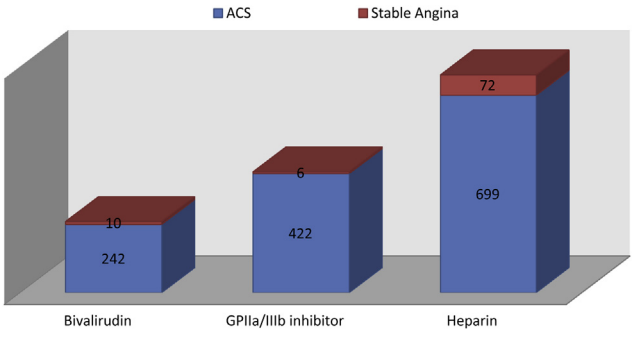

Fig. 1 – Distribution of patients with angina and ACS.

Table 4 – Anti-platelet use.

Treatment arm	Clopidogrel	Prasugrel	Ticagrelor	Total
Bivalirudin	119 (47.2%)	95 (37.7%)	38 (15.8%)	252
Heparin + GPI	350 (81.4%)	74 (17.2%)	6 (1.4%)	430
Heparin	656 (85.1%)	96 (12.4%)	19 (2.5%)	771

Table 5 – Patient distribution based on clinical condition.

Condition	Bivalirudin	Heparin+GPI	Heparin	Chi square	*p* value
Stable angina	10 (4.00%)	6 (1.40%)	72(9.30%)	28.8	<0.001
STEMI	49 (19.40%)	94 (21.90%)	105 (13.60%)	12.57	0.001
NSTEMI	7 (2.80%)	23 (5.30%)	24 (3.10%)	4.43	0.1
Unstable angina	140 (55.60%)	242 (56.30%)	570 (73.90%)	17.74	0.0001

Table 6 – Bleeding incidences.

Treatment groups	Bivalirudin	Heparin+GPI	Heparin	*p* value
Major bleeding	4 (1.59%)	3.15 (3.49%)	46 (5.97%)	<0.005
Major bleeding in STEMI patients	0 (0%)	7 (7.40%)	7 (14.3%)	<0.001
Access site bleeding	2 (0.79%)	7 (1.63%)	23 (2.98%)	0.1
Non access site bleeding	2 (0.79%)	8 (1.86%)	23 (2.98%)	

6. Discussion

Bivalirudin (Angiomax) was launched by Medicines Company in USA in 2001. However it was made available in India only in late 2011. Most of the published clinical trials have compared Bivalirudin with Heparin plus GPI and the results have been shown to be largely in favor of Bivalirudin both for In-hospital outcomes as well as long term benefits. The economic analysis from larger registry data base in US and also some large randomized trials also point out the economic benefit of using Bivalirudin in PCI. Recently published meta-analysis has shifted the focus of comparing the Bivalirudin outcomes against Heparin Monotherapy. All these data has been generated in a Western Healthcare system which works very differently compared to an Indian Healthcare System. The present study was carried out with an aim to compare antithrombotic strategy adopted at a tertiary care hospital in New Delhi. We compared the outcomes in an all comer population of patients undergoing PCI with Bivalirudin, Heparin plus GPI and Heparin monotherapy. This reflects a true Indian setting where there are multiple factors that govern the choice of drugs used in PCI. We also compared our data with some other published studies and registries and found it comparable to studies like ACTION registry,[11] Rassen et al.[12] We found mean age in Bivalirudin arm was 61.1 years, 59.5 years in Heparin plus GPI arm and 61.3 years in Heparin alone arm which were statistically similar in all the arms. Moreover, it was observed that 47.6% patients in Bivalirudin arm were diabetic. This was more when compared to UFH (41.1%) and GPI (12%). In addition, there were more male diabetic patients in each arm compared to female diabetic patients. Hypertension was seen in 61.16% in Heparin plus GPI arm, 59.9% in Heparin arm and 60.31% in Bivalirudin arm.

In Heparin group, 85.1% patients were on Clopidogrel while in Bivalirudin group, 47.2% were on Clopidogrel. The EUROMAX[13] study comparing Bivalirudin with Heparin and optional GPI in STEMI patients reflected the change in use of anti-platelet agents. In EUROMAX, almost 50% of the patients were treated with Prasugrel or Ticagrelor and 50% of the patients received clopidogrel both in Bivalirudin arm as well as Heparin with optional GPI. In our study, 37.7% and 15.1% patients were treated with Prasugrel and Ticagrelor respectively in Bivalirudin arm and 12.4% and 2.5% in Heparin arm. In EUROMAX study Prasugrel was used in 33.5% in Bivalirudin arm and 30.8% in Heparin with optional GPI. Ticagrelor was used in 26.9% in Bivalirudin arm and 26.7% in Heparin with optional GP IIb/IIIa inhibitor. This reflects an early stage of adoption of newer Anti-platelet drug in our Institute.

Major bleeding was reported as 1.59% in Bivalirudin arm, 3.49% in Heparin plus GPI and 5.97% in Heparin arm. Access site bleeding was 0.79% in Bivalirudin treatment group, 1.62% in Heparin plus GPI and 2.98% in Heparin arm. This represented an absolute reduction of 4.5% bleeding with Bivalirudin compared to UFH and an absolute reduction of 2% compared to GPI. The relative risk reduction was 73% compared to UFH and 54% compared to GPI. In addition, the patients on UFH required more blood transfusions compared to the patients who were on Bivalirudin thus resulting in more cost effectiveness of using an 'expensive' Bivalirudin. In current study, Abciximab was the most common GPI. Our results of lower

Table 7 – Cost effectiveness analysis.

	Bivalirudin ($n = 252$)	Heparin + GPI ($n = 430$)	Heparin ($n = 771$)
Mean cost of blood product transfusions (INR)	111.11	308.98	373.54
Cost incurred after adding anti thrombotic therapy	16693	10440	1307
Number of blood transfusion	4	25	38
Percentage of blood transfusion (%)	1.6	5.8	5
Cost of treatment per patient requiring blood transfusion	171.42	476.88	600.25
Total cost per patient with anti thrombin and blood transfusion	16753.31	10916.88	1907.25
Cost comparison Bivalirudin vs. Heparin + GPI	$Z = -2.25$; p value = 0.01		
Cost comparison Bivalirudin vs. Heparin Monotherapy	$Z = -3.23$; p value = 0.001		

bleeding including access site and non-access site bleeding with Bivalirudin as compared to Heparin with or without GPI is consistent with the literature.[14] Though, these results are contrary to the results of HEAT-PPCI study that suggested bleeding rates of Heparin alone are not different from those of Bivalirudin.[15] All-cause mortality within 1 month was 2.8% in Heparin plus GPI, 0.1% in Heparin, There was no death reported in Bivalirudin. Early definite stent thrombosis was seen in one patient in Heparin plus GPI, and none in Heparin alone arm. In EUROMAX study, definite stent thrombosis was seen in 1.6% cases in Bivalirudin arm and 0.2% in Heparin with optional GPI. In EUROMAX trial, patients treated with Bivalirudin were at higher risk for acute stent thrombosis, an observation consistent with the results of HORIZONS-AMI.[16–18] The increased risk for acute stent thrombosis was limited to the first 4 h after the index procedure and was probably the result of the combination of the short half-life and rapid clearance of Bivalirudin and the delayed bioavailability of the oral P2Y12 inhibitors, including the newer agents Prasugrel and Ticagrelor. Another reason for higher stent thrombosis in EUROMAX study was the lower dose of Bivalirudin infusion (0.25 mg/kg/hour) post procedure. In FEHI, we give a regular PCI dose infusion of Bivalirudin and run the bag out. A recent study from China BRIGHT[19] using similar Bivalirudin protocol also did not show increase in stent thrombosis while maintaining lower bleeding rates.

Possible treatments that could mitigate the reported risk of stent thrombosis could include co-administration of UFH, prolongation of the Bivalirudin infusion at the PCI dose for the first few hours after the procedure, or the use of an immediate acting P2Y12 inhibitor such as Cangrelor; however, they will need to be tested in prospective trials. In our study none of the patients underwent TLR & TVR within 30 days post procedure other than one early stent thrombosis reported with Heparin plus GP IIb/IIIa inhibitors.

Mean cost of blood product transfusions was INR 111.11 in Bivalirudin treatment group, INR 308.98 with Heparin plus GPI and INR 373.54 with Heparin alone. Initial cost of blood product transfusion was lower with Bivalirudin when compared to Heparin plus GPI arm. But, after adding, the acquisition cost of anti-thrombotic therapy and stay in hospital, the treatment cost increased to INR 16, 693 with Bivalirudin, INR 10, 440 with Heparin plus GPI and INR 1307 with Heparin alone. Though the cost of Bivalirudin increases the cost of overall cost of treatment, the benefits on account of lesser blood transfusion and reduced hospital stay still outweigh the incremental costs of drug acquisition.

7. Limitations

The study was a single centre study and open label study. Additional data to show the cost effectiveness of Bivalirudin in Stable angina patients should be generated and analyzed. Long term benefit of newer Anti-Thrombotic agents should be further evaluated. The practice patterns at other Indian institutions may not necessarily represent practice patterns at FEHI.

8. Conclusion

Use of Bivalirudin in all elective PCI should be considered and further data needs to be analyzed/generated. Bivalirudin can be safely adopted into Institutional protocol for the treatment of high risk PCI such as STEMI, ACS and complex elective PCI. Bivalirudin use during PCI is associated with a distinct advantage of having lower access site and non-access site bleeding without compromising on the overall efficacy. There was a reduction in number of blood transfusions, hospital stay and in short-term mortality for patients treated with Bivalirudin compared with Heparin plus GP IIb/IIIa inhibitors. The lower peri-procedural myocardial damage rates associated with PCI in the Bivalirudin group would improve outcomes in patients undergoing high risk PCI. Use of newer anti-platelet drugs should be encouraged in a real world setting with Bivalirudin.

Conflicts of interest

The authors have none to declare.

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