A comparison of bivalirudin to heparin with protamine reversal in patients undergoing cardiac surgery with cardiopulmonary bypass: The EVOLUTION-ON study

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Objectives: Unfractionated heparin and its antidote, protamine sulfate, allow for rapid and reversible anticoagulation during cardiac surgery with cardiopulmonary bypass, yet limitations exist, including a variable dose-response, dependence on a cofactor for anticoagulant effect, and antigenic potential. This trial was performed to evaluate the safety and efficacy of bivalirudin as an alternative to heparin with protamine reversal in on-pump cardiac surgery.

Methods: We conducted a randomized, open-label, multicenter trial comparing heparin with protamine reversal to bivalirudin in patients undergoing cardiac surgery with cardiopulmonary bypass. The primary objective was to demonstrate comparable rates of in-hospital procedural success defined as freedom from death, Q-wave myocardial infarction, stroke, or repeat revascularization. Twenty-one institutions enrolled 101 patients randomized to bivalirudin and 49 patients to heparin treatment.

Results: The primary end point of procedural success was not significantly different between the bivalirudin arm and the heparin/protamine arms at 7 days, 30 days, or 12 weeks' follow-up. Adequate anticoagulation was achieved in all patients. Secondary end points including mortality, 24-hour blood loss, overall incidence of transfusions, and duration of surgery were similar between the two arms.

Conclusions: Bivalirudin is a safe and effective anticoagulant for patients undergoing a wide range of cardiac surgical procedures with cardiopulmonary bypass. Procedural success rates with bivalirudin were similar to rates in patients receiving heparin anticoagulation, with no difference in mortality. Avoidance of blood stasis and attention to the intraoperative medical management of patients is critical for successful use of bivalirudin during cardiopulmonary bypass.

Unfractionated heparin (UFH) has been a cornerstone of cardiac surgery since the first operation using cardiopulmonary bypass (CPB), and while dramatic advances in surgical technique, anesthesia care, and perfusion technology have occurred since the early days of cardiac surgery, anticoagulation strategies have not changed. UFH and its antidote, protamine sulfate, allow for rapid and reversible anticoagulation, yet limitations exist. UFH requires a cofactor (antithrombin) for effect, resulting in variable patient response, heparin resistance, and

Abbreviations and Acronyms

ACT	= activated clotting time
CABG	= coronary artery bypass grafting
CPB	= cardiopulmonary bypass
EVOLUTION-ON	= <i>E</i> valuation of Patients during Coronary Artery Bypass Graft Operation: <i>L</i> inking <i>U</i> tilization of Bivalirudin to <i>I</i> mproved Outcomes and <i>N</i> ew Anticoagulant Strategies
HIT/TS	= heparin-induced thrombocytopenia and thrombosis syndrome
MI	= myocardial infarction
UFH	= unfractionated heparin

depletion of antithrombin during bypass, which is associated with poorer outcomes in patients undergoing cardiac surgery.^{1,2} UFH is also highly antigenic, provoking an antibody response in approximately 40% of patients after cardiac surgery and heparin-induced thrombocytopenia and thrombosis syndrome (HIT/TS) in 1% to 2% of patients.³ The variable and dose-dependent clearance of UFH requires reversal with protamine sulfate, which is antigenic as well.⁴⁻⁶ Protamine administration may result in clinical adverse reactions, including systemic hypotension, pulmonary hypertension, or anaphylaxis.⁵⁻⁸

Bivalirudin is a bivalent, reversible direct thrombin inhibitor with a relatively short half-life and is eliminated mainly by a proteolytic mechanism independent of renal or hepatic function. In several large trials, bivalirudin has been successfully used as a replacement for heparin during percutaneous coronary intervention.⁹⁻¹¹ During “off-pump” coronary artery bypass graft (CABG) surgery, the use of bivalirudin was associated with a comparable safety profile but improved graft patency rates compared with heparin and protamine reversal.¹² Moreover, in a prior pilot investigation in patients undergoing elective on-pump CABG surgery, the feasibility of bivalirudin for anticoagulation during CPB has been established.¹³ Bivalirudin, a 20 amino acid peptide with little secondary structure, appears to be nonimmunogenic.^{3,14,15}

The *E*valuation of Patients during Coronary Artery Bypass Graft Operation: *L*inking *U*tilization of Bivalirudin to *I*mproved Outcomes and *N*ew Anticoagulant Strategies (EVOLUTION-ON) trial was designed as a safety study to compare systemic anticoagulation with bivalirudin to UFH with protamine reversal in patients undergoing cardiac surgery with CPB. The study is a component of a larger program investigating the use of bivalirudin in patients undergoing on-pump and off-pump cardiac surgery, including those with HIT/TS or at risk for HIT/TS.

Methods**Study Population**

This was a randomized, prospective, multicenter, open-label, active-controlled study of bivalirudin versus UFH with protamine reversal in patients undergoing cardiac surgery with planned CPB. Patients underwent a variety of procedures, including primary and reoperative CABG, CABG plus valve surgery, or isolated valve surgery. Although patients with severe renal failure were excluded, patients with renal impairment (creatinine clearance ≥ 30 mL/min) were allowed. Patients recently exposed to preoperative anticoagulant medications including glycoprotein IIb/IIIa receptor antagonists, adenosine diphosphate receptor antagonists, low-molecular-weight heparins, or thrombolytics were excluded. The study was approved by the institutional review board at each site. Informed consent was obtained from 150 patients at 21 sites in the United States and Germany. A computerized telephone system was used to randomize patients to bivalirudin versus heparin/protamine with a 2:1 ratio; 101 patients were randomized to bivalirudin and 49 patients to heparin/protamine. Three patients dropped out of the bivalirudin arm after randomization but before surgery and were reassigned to receive heparin. Accordingly, 98 patients received bivalirudin and 52 patients received heparin as the sole anticoagulant during cardiac surgery with CPB. Data and summary statistics are presented on the basis of this safety population.

Clinical End Points

The primary end point of the study was in-hospital procedural success, defined as the absence of death, Q-wave myocardial infarction (MI), stroke, or repeat coronary revascularization. Secondary end points included non-Q-wave MI, transfusion requirements, major bleeding, thromboembolic events, change in renal function, and anticoagulation profile. Non-Q-wave MI was defined as creatine kinase MB elevation 10 times or greater than the local upper limit of normal if within 24 hours after surgery. If more than 24 hours after cardiac surgery, the definition was creatine kinase MB elevation greater than the upper limit of normal on 2 successive samples, or creatine kinase MB greater than 2 times the upper limit of normal on 1 occasion; and either ischemic symptoms or electrocardiographic changes indicative of ischemia. Adjudicated data from an independent and blinded clinical events committee are used in all statistical analyses. Major bleeding was defined as any intracranial or intraocular bleed, retroperitoneal bleeding, gastrointestinal bleeding, or persistent hemorrhage necessitating re-exploration.

Dosing and Monitoring of Anticoagulation

For patients randomized to heparin/protamine, individual institutional practices regarding dosing and protamine reversal were used. A summary of heparin and protamine doses are provided in [Table 1](#).

For patients randomized to bivalirudin, a 1.0 mg/kg intravenous bolus followed by a 2.5 mg $\cdot$ kg⁻¹ $\cdot$ h⁻¹ infusion was used. Timing of anticoagulation was routine and given at the request of the surgeon when systemic anticoagulation was desired. The bivalirudin infusion dose was not titrated during CPB, although additional boluses (0.1-0.5 mg/kg) were allowed at the discretion of the team. Total bivalirudin doses are detailed in [Table 1](#). An additional 50 mg of bivalirudin was added to the priming solution of the CPB

TABLE 1. Summary of drug administration

	Bivalirudin; N = 98 (mg/kg)	Heparin + protamine; N = 52 (units/kg)
Initial bolus dose		
Mean $\pm$ SD	1.0 $\pm$ 0.0	344.2 $\pm$ 101.3
Median	1.0	343.5
(minimum, maximum)	(1, 1)	(57, 615)
Initial infusion rate		
Mean $\pm$ SD	2.5 $\pm$ 0.2	0
Median	2.5	0
(minimum, maximum)	(1, 3)	
Total bolus dose		
Mean $\pm$ SD	1.0 $\pm$ 0.1	440.5 $\pm$ 209.1
Median	1.0	401.1
(minimum, maximum)	(1, 2)	(143, 1442)
Total drug dose*		
Mean $\pm$ SD	5.0 $\pm$ 1.6	440.5 $\pm$ 209.1
Median	4.5	401.1
(minimum, maximum)	(2, 9)	(143, 1442)
Total protamine dose		(mg/kg)
Mean $\pm$ SD	N/A	3.7 $\pm$ 1.5
Median	N/A	3.6
(minimum, maximum)		(0, 7)

Initial and total anticoagulation doses are detailed for patients receiving heparin/protamine and bivalirudin. Total dosing reflects additional boluses received during cardiopulmonary bypass. *SD*, Standard deviation; *N/A*, not available. *Includes 50 mg administered as the pump prime.

pump. Sodium citrate was the anticoagulant used in the cell salvage device in both groups.

Anticoagulation was monitored at baseline, within 5 minutes of drug administration, and thereafter according to standard institutional practice regarding the type and frequency. For patients receiving bivalirudin, an initial activated clotting time (ACT) 2.5 times the baseline was used as a guideline, based on the clotting test routinely used by the institution. Additional bolus dosing was left to the discretion of the surgeon and anesthesiologist.

Statistical Analysis

The study was designed to evaluate the safety of bivalirudin as an anticoagulant for patients undergoing cardiac surgery. Data were collected by The Medicines Company (Parsippany, NJ). Authors had full access to all data and were responsible for its interpretation, with approval rights over publication. All analyses were performed primarily on the “as-treated” (safety) population, defined as patients categorized according to the anticoagulant received, irrespective of randomization. Descriptive statistics were used to summarize most of the data. Quantitative (continuous) variables were summarized by mean, standard deviation, median, interquartile range, and minimum and maximum values. Qualitative (categorical) variables were summarized by frequencies and percentages. Owing to the small number of patients in each group, exploratory nonparametric tests (Fisher exact test for categorical variables, Wilcoxon rank-sum test for continuous variables) were used to calculate *P* values.

TABLE 2. Demographics, pertinent medical history, and procedures performed

Parameter	Bivalirudin (N = 98)	Heparin + protamine (N = 52)
Age (y); mean $\pm$ SD	63.9 $\pm$ 11.0	65.1 $\pm$ 9.8
Age group, n (%)		
<65 y	48 (49.0)	24 (46.2)
$\geq$ 65 y	50 (51.0)	28 (53.8)
Age group, n (%)		
<75 y	83 (84.7)	42 (80.8)
$\geq$ 75 y	15 (15.3)	10 (19.2)
Sex, n (%)		
Male	78 (79.6)	36 (69.2)
Female	20 (20.4)	16 (30.8)
Weight (kg)		
Mean $\pm$ SD	87.8 $\pm$ 15.0	85.5 $\pm$ 20.4
Median	85.5	86
(minimum, maximum)	(56, 128)	(45, 141)
Medical history		
Presented with angina, n (%)	69 (70.4)	26 (50.0)
Stable, n/N (%)	27/69 (39.1)	10/26 (38.5)
Unstable, n/N (%)	42/69 (60.9)	16/26 (61.5)
History of MI, n (%)	18 (18.4)	14 (26.9)
Prior PCI procedure, n (%)	20 (20.4)	13 (25.0)
Congestive heart failure, n (%)	15 (15.3)	9 (17.3)
Diabetes, n (%)	36 (36.7)	15 (28.8)
Isolated CABG	70 (71.4%)	35 (67.3%)
No. of grafts	N = 85	N = 46
Mean $\pm$ SD	3.2 $\pm$ 1.0	3.0 $\pm$ 1.0
Median	3.0	3.0
(minimum, maximum)	(1, 5)	(1, 5)
Combined CABG/valve operation	10 (10.2%)	8 (15.4%)
CABG/AVR prosthesis	5	4
CABG/AVR repair	0	1
CABG/MVR prosthesis	2	2
CABG/MVR repair	3	1
Any CABG LITA use rate	73/87 (84%)	39/44 (89%)
Isolated valve operation	12 (12.2%)	6 (11.5%)
AVR	10	3
MVR	2	3
Other	6 (6.1%)	3 (5.8%)

Patients were evenly matched between groups. In both groups, the number of men predominated. The incidence of significant comorbidities was similar between groups. *SD*, Standard deviation; *MI*, myocardial infarction; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass grafting; *AVR*, aortic valve replacement; *MVR*, mitral valve replacement; *LITA*, left internal thoracic artery.

Results

Results are presented for the safety population of this trial; intent-to-treat analysis provided very similar results. Demographic and medical history data are presented in Table 2. Median age between the two groups was similar, with a slightly higher percentage of women in the heparin/protamine arm than in the bivalirudin arm. The incidence of

TABLE 3. Intraoperative details

Parameter	Bivalirudin (N = 98)	Heparin + protamine (N = 52)
Duration of surgery (min)*	N = 98	N = 52
Mean $\pm$ SD	243.7 $\pm$ 91.7	241.7 $\pm$ 99.1
Median	229.0	220.5
(minimum, maximum)	(113, 665)	(111, 540)
Duration on CPB	N = 7	N = 50
Mean $\pm$ SD	85.3 $\pm$ 37.4	89.0 $\pm$ 51.2
Median	75.0	76.0
(minimum, maximum)	(30, 194)	(27, 365)
Crossclamp time	N = 94	N = 49
Mean $\pm$ SD	61.9 $\pm$ 23.6	67.7 $\pm$ 28.2
Median	58.0	68.0
(minimum, maximum)	(23, 123)	(27, 181)
Duration from end of CPB to chest closure†	N = 97	N = 50
Mean $\pm$ SD	71.2 $\pm$ 40.1	56.6 $\pm$ 29.3
Median	60.0	50.5
(minimum, maximum)	(21, 290)	(21, 175)

Coronary artery bypass grafting was the most common procedure in both groups. The duration of cardiopulmonary bypass (CPB) and the crossclamp time was similar between groups. While the time from the end of CPB to chest closure was longer in the bivalirudin group, the overall duration of surgery was similar. *SD*, Standard deviation. *Start of surgery to operating room exit. †*P* = .015. All other *P* values = not significant.

comorbid risk factors was comparable between groups. Approximately 70% of patients in both groups underwent isolated CABG. Table 2 provides a summary of procedures performed. Crystalloid cardioplegia was used in 25 patients

Figure 1. Procedural success. Procedural success, defined as the freedom from death, Q-wave MI, stroke, or revascularization, was not significantly different between groups at 7 days, 30 days, or 12 weeks after surgery.

Figure 2. Perioperative MI. Although fewer patients receiving bivalirudin had an MI, the study was not adequately powered to detect a difference in rates of MI between groups. The incidence of perioperative Q-wave and non-Q-wave MI was not significantly different between patients receiving with heparin (*Hep*) or bivalirudin (*Biv*) anticoagulation.

(48%) receiving heparin and 52 patients (53%) receiving bivalirudin. A blood-based cardioplegic solution was used in 24 patients (46%) receiving heparin and 42 patients (43%) receiving bivalirudin; the type of cardioplegia used in the remainder is unknown. The duration of CPB was similar between groups (Table 3). The time interval from the end of CPB until chest closure was longer in patients receiving bivalirudin anticoagulation (71.2 vs 56.6 minutes, *P* = .015), although the total operative time was not different between groups. Additional intraoperative details are outlined in Table 3.

The primary end point of procedural success was not significantly different between the bivalirudin arm and the heparin/protamine arms at 7 days, 30 days, or 12 weeks (Figure 1). Thirty-day mortality was also not significantly different between groups, with 3 deaths in the bivalirudin arm (3.1%; attributed to coronary artery disease, cardiac tamponade, and multisystem organ failure) and 1 death in the heparin/protamine arm (1.9%; attributed to right atrial and inferior vena cava disruption). One additional patient in the heparin/protamine arm died after 30 days, such that the 12-week mortality was 3.1% in the bivalirudin group and 3.9% in the heparin/protamine group.

Six patients in the bivalirudin group and 6 patients in the heparin group (6.1% vs 11.5%; *P* = .34) had a perioperative MI 7 days after surgery (Figure 2). The incidence of Q-wave MI (1/98 [1.0%] vs 1/52 [1.9%]; *P* = .999) was similar

Figure 3. Postoperative chest tube output. Median and mean postoperative chest tube output was higher for the bivalirudin treatment group at 2 hours ($P = .0009$) and was not significantly different between groups at 24 hours ($P = .13$), although significant variability existed and outliers were present in both groups.

between patients receiving bivalirudin or heparin, respectively. There was a numerically lower incidence of non-Q-wave MI in patients receiving bivalirudin compared with heparin (5.1% vs 9.6%; $P = .32$), although this difference was not statistically significant. Thirty-day and 12-week MI event rates were similar to those at 7 days. The incidence of stroke was also similar between the bivalirudin and heparin groups (1.1% vs 2.0% at 30 days and 12 weeks).

Cumulative blood loss at 2 and 24 hours postoperatively is detailed in Figure 3. Early median blood loss was 78 mL higher in patients receiving bivalirudin for anticoagulation compared with heparin/protamine (238 mL vs 160 mL; $P = .0009$). However, by 24 hours this difference was no longer statistically significant (793 mL vs 668 mL; $P = .15$). In addition, there was significant heterogeneity between clinical sites in the volume of postoperative blood loss. Using the predetermined definition, major bleeding occurred in 6% of patients receiving bivalirudin and 2% of patients receiving heparin/protamine ($P = .67$). This difference was driven by the difference in postoperative re-exploration between the bivalirudin and heparin/protamine groups (6/98 [6.1%] vs. 1/52 [1.9%]; $P = .67$). For patients undergoing CABG only, there was no difference in major bleeding between groups (2/75 [2.7%] vs 1/38 [2.6%]; $P = .999$, bivalirudin vs heparin, respectively). There was no difference in intracranial, gastrointestinal, intraocular, or retroperitoneal bleeding between groups.

The incidence of perioperative complications was low and similar between groups. The incidence of transfusion was not different between groups (Table 4). A total of 57 patients (58%) receiving bivalirudin and 31 (60%) patients receiving heparin/protamine received any transfusion during their hospitalization. Although significant variability

existed among clinical sites, the median number of packed red blood cell units transfused per patient was 1.0 unit higher in patients receiving bivalirudin anticoagulation. The incidence of platelet transfusion was also higher in patients receiving bivalirudin anticoagulation (Table 4), although this difference was not statistically significant ($P = .86$).

Bivalirudin was an effective anticoagulant during CPB. The 1.0 mg/kg bivalirudin bolus and 2.5 mg · kg⁻¹ · h⁻¹ infusion resulted in a rapid and sustained increase in ACT. Fewer patients required reloading after the initial bolus in the bivalirudin group than in the heparin group (9.2% vs 38.5%). Eight patients (8.2%) received an additional bolus of bivalirudin during CPB and the infusion was adjusted in

TABLE 4. Summary of transfusion requirements

	Bivalirudin; N = 98; n (%)	Heparin + protamine; N = 52; n (%)
Patients who had any transfusion	57 (58.2)	31 (59.6)
Transfusion product		
PRBCs	56 (57.1)	27 (51.9)
Platelets	19 (19.4)	5 (9.6)
Fresh frozen plasma	27 (27.6)	12 (23.1)
Other	7 (7.1)	3 (5.8)
Patients who received PRBCs ≥2 units	50 (51.0)	23 (44.2)
Patients with repeat exploratory operations	6 (6.1)	1 (1.9)

Transfusion practices were left to the discretion of the surgical team. A significant number of patients in both groups received a transfusion, although the incidence was similar. The re-exploration rates were not significantly different between groups. PRBC, Packed red blood cell.

7 (7.1%) patients. No incident of thrombosis within the oxygenator, arterial line, or cardioplegia line occurred in the study. In 2 patients receiving bivalirudin anticoagulation, clot formation was observed within the venous reservoir, with no adverse consequences. In 6 cases, clot formation was observed in the cell salvage device (separate from the CPB circuit). Atrial fibrillation was reported in 9.6% of patients receiving heparin and 9.2% of patients receiving bivalirudin. Acute renal failure occurred in 2 patients in the heparin and bivalirudin groups, respectively (3.8% vs 2.0%).

Discussion

EVOLUTION-ON is the first prospective, randomized trial demonstrating similar efficacy and safety using an alternative anticoagulant for patients undergoing cardiac surgery with CPB. Our data provide further convincing evidence for the feasibility for anticoagulation with bivalirudin during cardiac surgery with CPB. Procedural success rates with bivalirudin were similar to the rates with anticoagulation with heparin and protamine reversal, and the use of bivalirudin as the sole anticoagulant during CPB did not adversely affect mortality at 7 days, 30 days, or 12 weeks. Similarly, perioperative MI and other complications were not significantly different between groups at 7 and 30 days after surgery.

Although the incidence of MI between groups did not reach statistical significance, numerically fewer non-Q-wave MIs were present in patients receiving bivalirudin. Recent data have demonstrated that the magnitude of biomarker release after surgery correlates with outcomes and are more predictive of serious adverse outcomes than the presence of new Q waves.^{16,17} Additionally, heparin directly activates platelets¹⁸ and potentiates platelet activation, which may be problematic in patients with acute coronary syndromes requiring surgery.¹⁹ Whether the more predictable thrombin inhibition afforded by bivalirudin results in less myocardial injury during CABG with CPB requires further investigation.

Anticoagulation with bivalirudin was predictable and consistent. The reliable pharmacokinetic profile of bivalirudin was exemplified by the low number of patients requiring reloading or adjustment of infusion during CPB, and no patient in either group had difficulties with clot formation within the oxygenator or arterial side of the pump circuitry. In areas of stasis or in areas isolated from the circuit, bivalirudin levels may be depleted owing to metabolism by thrombin. Efforts to reduce stasis within the venous reservoir (such as the use of a closed system or temporary blood storage within citrate-phosphate-dextrose bags) can be effective strategies to assure adequate levels of bivalirudin and prevent clot formation. The use of bivalirudin as an anticoagulant in the cell salvage device has not been evaluated.

The choice of ACT instrument and type of test was left to the institution and included Hemochron ACT kaolin (ITC, a subsidiary of Thoratec Corporation, Pleasanton, Calif), ecarin clotting time, ACT+, and ACT-T. All ACT tests used appeared to be effective tools for monitoring anticoagulation with bivalirudin. The initial bivalirudin bolus resulted in rapid prolongation of the ACT, which was maintained throughout the duration of CPB without the need for significant dose adjustment. This ability to successfully provide anticoagulation for patients with minimal variability allows for weight-based dosing with bivalirudin, in contrast to heparin. The ACT declined more rapidly after heparin reversal with protamine than with bivalirudin, as the majority of clearance of bivalirudin is through proteolytic cleavage. However, this did not adversely affect the duration of surgery (a difference of 8.5 minutes), and the median duration from the end of CPB to the end of surgery was also only 9.5 minutes longer in patients with bivalirudin anticoagulation. This was somewhat surprising, as more rapid hemostasis might be expected with heparin, given its immediate reversibility with protamine. The similar chest closure time may reflect the short half-life of bivalirudin, which differentiates it from other direct thrombin inhibitors.

Cumulative median blood loss within the first 24 hours was not excessive in either the heparin or bivalirudin group and was similar to other large, prospective, randomized trials in which postoperative bleeding was quantified.^{20,21} In patients receiving bivalirudin anticoagulation, there was increased blood loss (with significant variability) in the early postoperative period. Other early postoperative events such as platelet transfusion and re-exploration for persistent hemorrhage were more frequent in patients receiving bivalirudin, although the total number of patients was small and the differences in platelet transfusion and re-exploration rates were not statistically significant. Unfamiliarity with bivalirudin and the more gradual return to hemostasis in these patients may have triggered early platelet use. Other causative factors for early postoperative bleeding may include inappropriate reloading during CPB. However, the rates of platelet transfusion in both groups were in line with national norms: 0% to 36% as reported in a study of 24 academic institutions across the United States²² and 14.4% as reported in a study analyzing data from 6 double-blind aprotinin clinical trials performed for licensure.²³ Careful attention to the medical management and perfusion management of patients with bivalirudin anticoagulation could minimize early blood loss.

The limitations of the study include its small size and open-label design. No attempt was made to control transfusion triggers or clinical practice among sites.

Conclusions

Bivalirudin is a safe and effective anticoagulant for patients undergoing a wide range of cardiac surgical procedures with CPB. Procedural success rates with bivalirudin were similar to those with heparin anticoagulation. Patients receiving bivalirudin also had acceptable clinical outcomes, with no difference in mortality or complications after surgery. The trend toward fewer MIs in patients receiving bivalirudin suggests a need for further evaluation in adequately powered, prospective clinical trials. Although bivalirudin is an effective anticoagulant, its pharmacodynamic profile requires attention to medical management to reduce early postoperative bleeding and transfusion.

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