Evolving Technology

Anticoagulation with bivalirudin for off-pump coronary artery bypass grafting: The results of the EVOLUTION-OFF study

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Objectives: Unfractionated heparin has many shortcomings, including indirect and partial inhibition of thrombin, antibody formation, and platelet activation. Bivalirudin, a short-acting direct thrombin inhibitor, avoids these limitations and has superior outcomes during percutaneous revascularization. This trial was performed to evaluate the safety and efficacy of bivalirudin in off-pump coronary artery bypass grafting.

Methods: An open-label, multicenter randomized trial compared heparin with protamine reversal to bivalirudin in patients undergoing off-pump coronary artery bypass. The primary objective was safety as demonstrated by similar rates of procedural success defined as freedom from a composite of death, myocardial infarction, stroke, and repeat revascularization. Twenty-one institutions randomized 105 patients to receive bivalirudin and 52 patients to receive heparin.

Results: The mean age was 65 years for both groups. The bivalirudin group had more grafts: 3.0 ± 1 versus 2.5 ± 1. Procedural success rates at 30 days were identical in bivalirudin- and heparin-treated patients (93%). Operative times, total blood loss, reoperations for bleeding, and major adverse events were not significantly different. Strokes were more frequent in the heparin group: 5.5% versus 0; $P = .05$. Mortality was 2% in each group. Repeat revascularization was required in 3% of bivalirudin- and 2% of the heparin-treated patients.

Conclusions: For patients undergoing off-pump coronary artery bypass grafting, bivalirudin was an effective anticoagulant, without excessive bleeding and with a safety profile similar to that of heparin. Further trials are warranted to assess whether anticoagulation with bivalirudin improves clinical outcomes.

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The phenomenal growth and outstanding results of surgical and percutaneous vascular procedures attest to the utility of heparin, but limitations of this agent include incomplete anticoagulation, heparin resistance, and the increasingly relevant development of heparin antibodies. Bivalirudin, a reversible direct thrombin inhibitor with a short half-life, is an intriguing alternative to heparin and has properties that may improve outcomes.

Investigation of the utility of bivalirudin in cardiac surgery has followed clinical success with the drug in percutaneous interventions,[1] off-pump coronary bypass grafting (OPCAB), and off-label use of the drug for patients with heparin-induced thrombocytopenia (HIT).[1-3] In the REPLACE-2 trial of percutaneous coronary intervention, bivalirudin was statistically not inferior to heparin plus platelet glycoprotein IIb/IIIa blockade in reducing ischemic events and was associated with less

Abbreviations and Acronyms

ACT = activated clotting time
CABG = coronary artery bypass grafting
EVOLUTION = *EV*aluation of Patients during coronary artery bypass graft *O*perations: *L*inking *UT*ilization of bivalirudin to *I*mproved *O*utcomes and *N*ew anticoagulant strategies
HIT = heparin-induced thrombocytopenia
MI = myocardial infarction
OPCAB = off-pump coronary artery bypass grafting
REPLACE = Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events
TIMI = thrombolysis in myocardial infarction

bleeding.[1] Merry and colleagues[4] assessed the efficacy of bivalirudin in a 100-patient, randomized single institution OPCAB trial. Bivalirudin showed a safety profile similar to that of heparin with improved thrombolysis in myocardial infarction (TIMI) flow. An editorial[5] accompanying the publication by Merry and associates outlined the drug's potential advantages, including inhibition of clot-bound thrombin, slow reversal of anticoagulation, and possibly a reduced risk of developing HIT—a known risk factor for perioperative thrombotic complications.

The EVOLUTION (*EV*aluation of Patients during coronary artery bypass graft *O*perations: *L*inking *UT*ilization of bivalirudin to *I*mproved *O*utcomes and *N*ew anticoagulant strategies) trial is the first open-label multicenter controlled evaluation of a new anticoagulant as a potential alternative to heparin in patients undergoing OPCAB.

Patients and Methods

Study Design

This was an open-label study sponsored by the Medicines Company (Parsippany, NJ). Patients scheduled for elective OPCAB were randomized in a 2:1 ratio to bivalirudin or heparin. Excluded were patients with HIT (evaluated in a separate nonrandomized protocol), previous sternotomy, on dialysis, stroke within 6 months, those receiving warfarin, clopidogrel (within the prior 5 days), lepirudin, or agatroban (within the prior 24 hours), or with a known allergy to bivalirudin or hirudin-type drugs.

The primary objective was to assess the safety of bivalirudin as defined by the end points of death, Q-wave myocardial infarction (MI), repeat coronary revascularization and stroke (hemorrhagic and ischemic) at 7 days/discharge (primary end point), and at 30 days and 12 weeks (secondary end points). Non–Q-wave MI, bleeding outcomes, and other safety variables were also evaluated.

Definition of Variables

Death. All-cause through 12 weeks.

Q-wave MI. New Q wave of more than 0.04 milliseconds' duration or a depth greater than one fourth of the corresponding R-wave amplitude, or both, in 2 contiguous leads.

Non–Q-wave MI. Creatine kinase MB elevation of 10 times the upper limit of normal or greater and, after 24 hours, by creatine kinase MB greater than the upper limit of normal on 2 successive samples or greater than 2 times the upper limit on 1 occasion with evidence of ischemic symptoms or electrocardiographic changes of ischemia.

Incomplete revascularization. A vessel originally targeted for revascularization was not grafted.

Repeat coronary revascularization. Percutaneous or repeat surgical revascularization after OPCAB.

Stroke. Any cerebrovascular accident, ischemic or hemorrhagic, as recognized by change in neurologic status lasting at least 24 hours or leading to death.

Procedural success was defined by absence of death, Q-wave MI, repeat revascularization, or stroke at 7 days or discharge, at 30 days, and again at 12 weeks. Bleeding was analyzed separately. Volume of chest tube drainage, quantity of transfusions, and re-exploration for bleeding were examined. Major bleeding events were defined as intracranial, intraocular, retroperitoneal, or gastrointestinal bleeding that occurred within 7 days.

Statistical Method

The sample size was not powered to test a formal statistical hypothesis. Complications were analyzed by both the intention-to-treat population and the safety population (all patients who received drug, categorized by treatment received). No differences were found and results are presented for the safety population. Descriptive statistics were used to summarize most of the data. Quantitative (continuous) variables were summarized by mean, standard deviation, median, and interquartile ranges. Qualitative (categorical) variables were summarized by frequencies and percentages. Because of the small number of patients, exploratory nonparametric tests (Fisher exact test for categorical variables, Wilcoxon rank-sum test for continuous variables) were used to calculate *P* values. The raw data were supplied to the Cleveland Clinic Foundation for independent statistical analysis. There were no restrictions placed by the sponsor of the trial on publications or presentation of the trial's results.

Patients

A total of 157 patients were randomized at 21 centers. Of the 105 patients randomized to bivalirudin, 4 patients received only heparin because of surgeon preference (n = 1), necessity of valve intervention (n = 1), and exclusion criteria identified after randomization (n = 2). Two additional patients randomized and receiving bivalirudin required conversion to cardiopulmonary bypass; one received heparin and the other continued to receive bivalirudin. Of the 56 patients who received heparin (52 randomized + 4 as described above), 2 were converted to cardiopulmonary bypass and 1 was selected for valve intervention. The safety population, therefore, consisted of 101 patients receiving bivalirudin and 56 receiving heparin.

TABLE 1. Demographics at baseline

Demographics/baseline characteristics	Bivalirudin (N = 101)	Heparin (N = 56)
Age (y)		
Median	63	67
(Q1, Q3)	(56, 73)	(60, 73)
Male, n (%)	77 (76.2)	45 (80.4)
Medical history, n (%)		
History of MI	37 (36.6)	24 (42.9)
Prior PCI procedure	25 (24.8)	18 (32.1)
Congestive heart failure	13 (12.9)	5 (8.9)
Diabetes	31 (30.7)	18 (32.1)

MI, Myocardial infarction; *PCI,* percutaneous coronary intervention. All P = not significant.

TABLE 2. Summary of CABG surgery

Parameter	Bivalirudin (N = 101)	Heparin (N = 56)
Duration of operation (min)		
Median	189	192
(Q1, Q3)	(150, 238)	(141, 236)
No of grafts		
Mean ± SD	3.0 ± 1.0	2.5 ± 0.9*
Type of graft, n (%)		
LITA	98 (97.0)	52 (92.9)
RITA	4 (4.0)	2 (3.6)
Saphenous vein	88 (87.1)	43 (76.8)
Radial artery	22 (21.8)	10 (17.9)
Incomplete revascularization, n (%)	4 (4.0)	5 (8.9)
Use of aminocaproic acid or aprotinin, n (%)	48 (47.5)	18 (32.1)

CABG, Coronary artery bypass grafting; *SD,* standard deviation; *LITA,* left internal thoracic artery; *RITA,* right internal thoracic artery. *P = .003; all others: P = not significant.

Intraoperative Management

OPCAB technique was at the discretion of the surgeon. Centers were advised to avoid static columns of blood because of the metabolism of bivalirudin by thrombin, which could lead to local reduction in anticoagulation. Aprotinin (Trasylol; Bayer, Mannheim, Germany) or aminocaproic acid (Amicar; Wyeth, Madison, NJ) were used in 48% of the bivalirudin- and 30% of the heparin-treated patients.

Bivalirudin was given as a 0.75 mg/kg intravenous bolus and a 1.75 mg · kg^{-1} · h^{-1} infusion for the duration of the procedure, with the option to increase or decrease the infusion in 0.25 mg · kg^{-1} · h^{-1} increments or administer additional 0.1 to 0.5 mg/kg boluses to maintain an activated clotting time (ACT) greater than 300 seconds. Maintenance infusion was discontinued at the discretion of the cardiac surgeon and anesthesiologist, but was commonly stopped 15 minutes before flow would be restored down all grafts. Heparin was administered on a weight-adjusted basis to reach an ACT greater than 300 seconds. Protamine was given in all heparin-treated patients at a mean dose of 205 mg (range 15-450 mg); 14 patients received 100 mg or less of protamine.

Results

Baseline patient characteristics were similar (Table 1). The majority of patients received at least one internal thoracic artery graft. In the heparin group, significantly fewer bypass grafts were performed with a slightly higher rate of incomplete revascularization; nevertheless, the duration of the procedure was similar (Table 2). Composite and individual end points at 7 days/discharge, 30 days, and 12 weeks occurred infrequently and their rates were not significantly different (Table 3). Three strokes occurred, all in the heparin arm, representing a statistically significant difference between treatment groups (5.5% vs 0%; P = .05). All were ischemic and occurred at 3 and 7 days after the OPCAB. Repeat revascularization was required in 4 patients. One heparin-treated patient underwent repeat coronary artery bypass grafting (CABG) and thrombus was found in a vein graft to the distal right coronary artery. In the bivalirudin arm, 3 patients underwent percutaneous revascularization of left internal thoracic artery grafts to the left anterior descending artery, which were occluded at 2, 42, and 44 days after operation. Rates of Q-wave and non–Q-wave MI were similar between groups. All-cause mortality was low (2%) and identical between groups at 30 days and 12 weeks.

Bleeding complications and use of transfusion occurred at similar rates (Table 4, Figure 1). For patients who received a transfusion, those treated with bivalirudin received significantly more units of packed red blood cells (4.0 vs 2.3). Reoperation for bleeding was similar: bivalirudin 7.9% versus 5.4% for heparin. Although more aminocaproic acid and aprotinin was used in the bivalirudin arm, this use and the degree of heparin reversal with protamine did not affect the rates of bleeding, transfusion, or end points.

Discussion

This study was designed to assess the safety of bivalirudin in patients undergoing OPCAB in the general cardiac surgical community. In this setting, bivalirudin resulted in similar rates of major adverse events and bleeding at 7 days/discharge, 30 days, and 12 weeks when compared with heparin. OPCAB was initially studied to minimize the complexities of managing a new drug in both the operative field and bypass circuit.

Bivalirudin is a 20 amino acid synthetic peptide that directly inhibits thrombin and has a short half-life. For anticoagulants to work effectively and safely during cardiac surgery, they must have a rapid onset of action, maintain a desired level of anticoagulation, and allow hemostasis once discontinued. Previous off-[2,4] and on-pump[3] series have suggested that bivalirudin fulfills all these requirements, and this was confirmed in this study.

Hemorrhagic complications occurred with equal frequency and blood loss was nearly identical to that in

TABLE 3. Summary of efficacy end points

	Day 7/discharge		30 days		12 weeks	
	Bivalirudin	Heparin	Bivalirudin	Heparin	Bivalirudin	Heparin
Primary and secondary efficacy end points						
Procedural success						
N	101	56	100	56	100	56
n (%)	97 (96.0)	53 (94.6)	93 (93.0)	52 (92.9)	93 (93.0)	52 (92.9)
Non–Q-wave MI						
N	101	56	99	55	99	55
n (%)	4 (4.0)	3 (5.4)	4 (4.0)	3 (5.5)	4 (4.0)	3 (5.5)
Clinical end points included in the composite end point procedural success						
Death						
N	101	56	100	56	100	56
n (%)	1 (1.0)	1 (1.8)	2 (2.0)	1 (1.8)	2 (2.0)	1 (1.8)
Q-wave MI						
N	101	56	98	55	98	55
n (%)	2 (2.0)	0 (0.0)	2 (2.0)	0 (0.0)	2 (2.0)	0 (0.0)
Repeat revascularization						
N	101	56	98	56	98	56
n (%)	1 (1.0)	1 (1.8)	3 (3.1)	1 (1.8)	3 (3.1)	1 (1.8)
Stroke						
N	101	56	98	55	98	55
n (%)	0 (0.0)	2 (3.6)	0 (0.0)	3 (5.5)*	0 (0.0)	3 (5.5)*

MI, Myocardial infarction. *$P = .05$.

Merry's bivalirudin group and similar to published data for OPCAB.[4] The reoperation rates of 7 % in the bivalirudin group and 6% in the heparin arm are higher than expected for OPCAB, and although more heparin patients were transfused, bivalirudin patients received more packed cells per transfusion episode. The vast majority of published reoperation rates are less than 3% although the reoperation rate in one series was 4% when patients having circumflex grafts or acute MIs were included.[7,8] The indication and threshold for reoperation for bleeding was not defined in the protocol, and this higher rate of reoperation is unlikely a lower tolerance for bleeding since the median blood loss in the patients taken back for bleeding exceeded that of those not taken back by almost 2 L. We could not find an obvious explanation for the high reoperation rates. Case clustering, use or nonuse of aminocaproic acid or aprotinin, incomplete reversal of heparin with protamine, and high intraoperative ACT in the bivalirudin group were not associated with bleeding. The possibility remains that the high rates of reoperation and need for transfusions in the heparin arm masked excessive bleeding in the bivalirudin group.

OPCAB has been associated with better myocardial protection as manifested by uniformly low creatine kinase release. Van Dijk and colleagues,[6] in a randomized trial of OPCAB compared with on-pump CABG, showed creatine kinase MB release was significantly lower at all time points from 2 to 20 hours after surgery in the OPCAB group. Definitions of MI have varied in different studies, but in general the rate has been less than 5% for OPCAB.[6-9] MIs in this trial occurred at rates that were comparable with prior OPCAB series. Almost twice as many bivalirudin patients received aminocaproic acid or aprotinin, but stratifying patients by use of these drugs did not affect the occurrence of MIs in either group.

The reintervention rate in the bivalirudin arm was 3%, which is comparable with published rates.[6-9] Loss of 3 left internal thoracic arteries to the left anterior descending artery in the bivalirudin group is concerning, but the number of events is too small to determine whether this is related to chance or possibly to how the conduit was handled or related to the drug itself. Theoretically, if the internal thoracic artery was detached from the chest wall for any period of time before flow was re-established through the graft, thrombus could potentially develop within the graft owing to metabolism of bivalirudin by thrombin within the stagnant blood column. The patency of the bypass grafts was not assessed by systematic angiography in this series, and in other series graft patency has been quite variable. Many have shown outstanding patency rates whereas others have shown decreased patency when OPCAB is compared with on-pump grafting. Khan and associates[8] recently published a randomized trial of OPCAB versus on-pump CABG in *The New England Journal of Medicine.* At 3 months, 82% of the patients underwent follow-up angiography. Patency was significantly reduced in the OPCAB group (88% vs 98% for on-pump). In Merry's trial,[4] 79% of patients re-

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TABLE 4. Summary of bleeding

	Bivalirudin (N = 101)	Heparin (N = 56)
Total blood loss postop (mL)		
N	101	55
Median	717	783
(Q1/Q3)	(475, 1190)	(528, 1032)
Maximum	15405	5610
Transfusion at day 7/discharge		
N	101	56
n (%)	46 (45.5)	33 (58.9)
Transfusion product by day 7/ discharge, n (%)		
N	101	56
PRBC	42 (41.6)	30 (53.6)
Platelets	13 (12.9)	5 (8.9)
Fresh frozen plasma	15 (14.9)	8 (14.3)
Total units/patient—PRBC by day 7/discharge*		
N	42	30
Median	4.0	2.3
(minimum, maximum)	(1.0, 19.0)	(1.0, 16.7)
Total units/patient—platelets by day 7/discharge		
N	13	5
Median	5.9	4.5
(minimum, maximum)	(1.0, 24.2)	(2.0, 10.0)
Total units/patient—fresh frozen plasma by day 7/discharge		
N	15	8
Median	3.3	3.0
(minimum, maximum)	(1.5, 26.0)	(1.0, 6.7)

PRBC, Packed red blood cells. *$P = .012$.

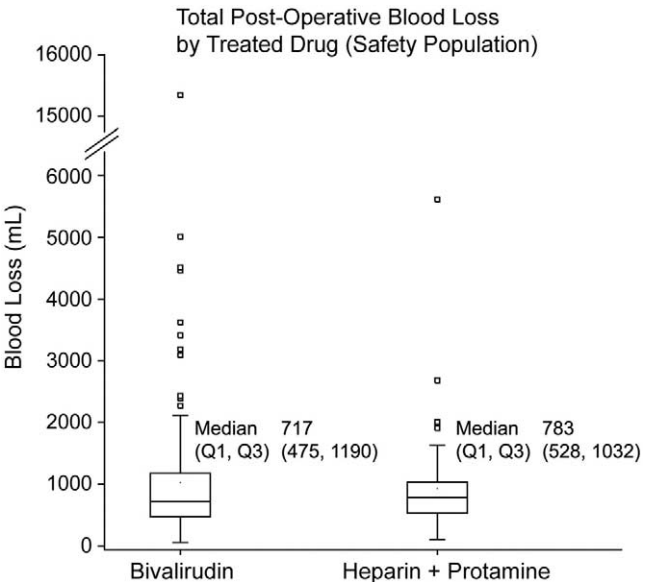

Figure 1. Total blood loss.

turned for follow-up angiography. The bivalirudin cohort had more grafts with normal flow than did the heparin group, 82% compared with 67%, and more patients in the bivalirudin arm had complete flow in all grafts; 60% versus 38%. A larger cohort of patients with follow-up angiography would need to be examined to determine whether bivalirudin affects graft patency.

One potential advantage of OPCAB is avoidance of cardiopulmonary bypass and aortic crossclamping. Despite this theoretical advantage, published series, including this one, have been too small to determine whether off-pump surgery actually reduces long-term neurologic event rates.[10] There were no strokes in patients receiving bivalirudin, and the 6% rate in the heparin arm is higher than the expected rate of around 2% from published series. An interesting finding is that the strokes occurred 3 or more days after surgery; whether such late events were related to arrhythmias such as atrial fibrillation or a prothrombotic state induced by heparin exposure warrants further investigation.

Limitations

This was a small pilot using a composite end point to assess safety. A large number of centers participated, many enrolling fewer than 15 patients, and intraoperative and postoperative management was left to the surgeon and center. This may have affected results in unpredictable ways, and improvement of these results can be expected with more experience. Because of the small number of patients, comparison of specific outcomes such as bleeding or strokes must be done cautiously and generalizations avoided. Without angiography, graft patency is unknown and any potential advantage of bivalirudin in this regard remains theoretical.

This multicenter trial provides further evidence to suggest that bivalirudin is a safe and effective alternative to heparin plus protamine for anticoagulation of patients undergoing OPCAB. Better understanding of the drug kinetics, the best method to monitor anticoagulation, and developing an effective method to reverse the anticoagulation effects without promoting thrombosis will enhance the safety profile. The efficacy of bivalirudin in on-pump surgery has been assessed in a separate trial. Future large-scale investigations will be necessary to evaluate the potential of bivalirudin to surpass heparin in regard to procedural success and reduction in cardiovascular complications. At the present time, bivalirudin has not been approved by the Food and Drug Administration for use in cardiac surgery.

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Appendix

The following institutions participated in the trial:

Germany: Berlin Heart Center, Berlin, Germany (n = 22).

New Zealand: Mercy Hospital/University of Auckland, Auckland, New Zealand (n = 1).

United States: VCU Health System/Medical College of Virginia, Richmond, Va (n = 3); Washington University School of Medicine/Washington University Medical Center, St Louis, Mo (n = 3); Comanche County Memorial Hospital, Lawton, Okla (n = 7); Enloe Medical Center, Chico, Calif (n = 4); Houston Northwest Medical Center, Houston, Tex (n = 38); Florida Heart Institute at Florida Hospital, Orlando, Fla (n = 10); Baylor University Medical Center, Dallas, Tex (n = 2); Charleston Area Medical Center (CAMC), Charleston, WVa (n = 20); Kaiser Permanente Medical Center, Honolulu, Hawaii (n = 5); New England Medical Center, Boston, Mass (n = 1); St Michael's Medical Center, Newark, NJ (n = 5); Washington Hospital Center, Washington, DC (n = 3); Sparks Regional Medical Center, Fort Smith, Ark (n = 2); Bassett Healthcare, Cooperstown, NY (n = 2); McGuire VA Medical Center, Richmond, Va (n = 1); VAMC, Washington, DC (n = 1); Banner Thunderbird Medical Center, Glendale, Ariz (n = 4); Nebraska Methodist Hospital, Omaha, Neb (n = 19); The Cardiopulmonary Research Science and Technology Institute (CRSTI), Dallas, Tex (n = 4).

Discussion

Dr John C. Chen *(Honolulu, Hawaii).* This prospective, open-label, multicenter clinical trial aims to compare the safety and effectiveness of bivalirudin versus heparin anticoagulation in patients undergoing CABG. The major potential advantages of the study medication are avoidance of HIT and protamine reactions. Although bivalirudin can be used on pump, OPCAB was initially studied to minimize the complexities of managing a new drug in both the operative field and bypass circuit.

Should studying first in off-pump surgery be a paradigm for pharmacologic CABG trials in the future?

Dr Smedira. It depends on what we are studying. Our idea was that the drug's mechanism of action was so different from that of heparin that we had to think through how we managed the operative field. The real concern was that any static columns of blood could potentially thrombose if that blood was not replenished with a new source of bivalirudin. Thus, do you disconnect the thoracic artery from the chest wall when you walk in the room or do you leave it intact to allow blood to flow through that? Do you do your proximal grafts first or your distal grafts? Where do you put the bulldog clamp? What do you flush with? If we are talking about a drug that requires a change in how we manage the intraoperative field, it may be something worth considering. That said, it turns out that the on-pump studies were straightforward to do and the drug was easy to use. We were very cautious because we thought that we could handle bleeding but that the loss of grafts or thrombosis of conduits would have been a major setback.

Dr Chen. This was an intention-to-treat pilot trial of 157 patients at 21 centers using a composite end point to assess safety. You chose to study a composite primary end point of death, Q-wave MI, repeat coronary revascularization, stroke, and bleeding within 7 days of surgery. Why did you decide on a composite end point with so many variables in the initial study design? I do not quite see the association between stroke within 7 days of surgery and the need for later repeat coronary revascularization.

Dr Smedira. One of the issues is that with such a small number of patients, if you do not define a series of end points you are not going to show any difference. We really needed to have a number of events to see whether we could determine a difference between the two groups. That is why we used the composite end points. That being said, some published data indicate that after exposure to heparin there is the development of a prothrombotic state, especially in the off-pump situation. You could argue that the strokes that we see postoperatively, and other events like loss of bypass grafts, may be related to a prothrombotic state and the composite end points of stroke, and need for revascularization may have been diminished by use of drugs that could potentially reduce these effects. Those are some theoretical arguments that have been touted as one of the potential advantages of this drug-that it doesn't induce a prothrombotic state after surgery.

Dr Chen. In the manuscript you noted that, despite significantly more aminocaproic acid and aprotinin use in the bivalirudin group versus the heparin group, transfusion rates were similar between the two groups. Do you have any insight as to the rationale for such a high percentage of antifibrinolytic drug use

among surgeons performing OPCAB? The percentages were 30% and 47%, I believe.

Dr Smedira. No, I don't know. The approach was left to the individual surgeon or center. It was higher than I would have expected and I don't know the rationale.

Dr Chen. My final question relates to a specific patient treated with bivalirudin. The manuscript lists and your slide illustrates a patient sustaining over 15 L of blood loss. Was this patient returned to the operating room for bleeding? If he was, what was found?

Dr Smedira. This unfortunate gentleman was in the operating room for 6 or 8 hours. From what I understand, they had great difficulty with the circumflex coronary artery during grafting, had a lot of bleeding, had to regraft it a number of times, and put a patch on it. Then they had difficulties with bleeding. He was returned to the intensive care unit and then to the operating room for re-exploration. It sounds like one of those nightmarish cases that occasionally occur. We did not think that it was directly related to the drug.

Dr Scott Rankin *(Nashville, Tenn).* Congratulations on an excellent study. There has always been a need to approach the HIT problem and I think your initial concept is a good one. It is also nice to see it being explored in a scientific way with randomized trials on the front end.

My question relates to the vascular occlusive phenomena that you see here, specifically potential differences in stroke rates with the bivaliruden group having a lower stroke rate postoperatively but having a higher thoracic artery occlusion rate. Do you think with a larger sample size that these phenomena may become statistically and clinically significantly different? On the basis of more detailed analysis of those specific cases, what do you think the significance of those phenomena is? For example, looking at the patients who had cerebrovascular disease preoperatively, was there any influence there? Examining the thoracic artery occlusions postoperatively, were they from dissections or did it look like it was a good anastomosis and just an in situ thrombosis? Do you have any more information on that?

Dr Smedira. Thank you. Your first question concerned whether, given more patients, we could potentially sort out whether the strokes and arterial occlusions are a real phenomena. Potentially, I think we could. I did look into the operative details on the occlusions and, from what I could discern from the intraoperative management and what was done and seen, it seemed like it was a straightforward case. There was no concern about the anastomosis, no concern about the flow or the integrity of the thoracic artery, and yet 3 were occluded within about 6 weeks. I wondered whether taking the thoracic artery down early and placing a bulldog clamp distally might have predisposed to the development of thrombosis within the wall. I think that is definitely a possibility. As a result, when I use the thoracic artery off-pump or even on-pump, I leave it in situ on the wall until right before I'm going to use it.

As for the strokes, it is so hard to tell. The study only looked at the occurrence of a neurologic event. It did not really go into great detail about the stroke. As I mentioned, one patient had to go on bypass urgently because of hypotension and was identified as having a stroke on day 3. They were not hemorrhagic, and we do not have a lot of details on the other two, so I do not know if that is a thrombotic issue related to heparin exposure and potential antibody formation or simply something like atrial fibrillation.

Dr Robert Guyton *(Atlanta, Ga).* I think it is a very important topic. Like others, we are using this when we need to in the OPCAB patients. My concern is similar to Dr Rankin's in that not only were there 3 occlusions but there was a 9% MI rate in the bivalirudin group. Are there data either from subparts of this series, institutions that did postoperative catheterization or from elsewhere, about graft patency in patients who have had bivalirudin. We have long been advocates of trying to get postoperative catheterizations whenever we use new techniques and generally have found that payers have been agreeable about paying for that 1-week postoperative catheterization. Are there any data in the literature about graft patency with bivalirudin?

Dr Smedira. We do not have any patency angiography data from this study, but we do have Alan Merry's study in New Zealand, in which he had angiograms on 60% to 70% of his patients who had bivalirudin. In fact, using a TIMI-1, 2, 3 classification, he found that patients receiving bivalirudin had better flow, more TIMI-3 flow in their grafts, than patients receiving heparin. This is intriguing and suggests that the patency is better with bivalirudin. As you know quite well, from John Puskas' data, the patency in a lot of OPCABG studies has been very good, 90% to 95% or better. However, we also have one study by Khan in *The New England Journal of Medicine* which shows that the patency of the internal thoracic artery in the off-pump group is a good 8% to 10% lower than in the on-pump group and overall patency was significantly less. This study has been criticized as coming from a center without a lot of experience with off-pump grafting. One possibility is that our study is a real-world phenomenon and displayed the type of patency one may see, regardless of which drug is used for anticoagulation, in centers that are not doing 100% of their cases off-pump.

Dr Joseph Cleveland *(Denver, Colo).* Given the observation that some of these thromboses were seen somewhat later, did you examine clopidogrel (Plavix) use in this group postoperatively? As you know, a lot of clopidogrel that is arbitrarily used for OPCAB patients as there are reports in the literature regarding a potential increased risk of thrombotic complications in this group of patients. Were there differences in the two groups with regard to clopidogrel exposure postoperatively and could differential clopidogrel exposure postoperatively account for some of these observed differences?

Dr Smedira. That is a great question. I don't know the answer to it, but that is something we can look into.