Bivalirudin in Peripheral Interventions

Results from the APPROVE trial and the emerging role of "endopharmacology" in treating PVD.

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Due to the increasing number of percutaneous peripheral interventions (PPIs) being performed each year, the need for a safe, reliable procedural anticoagulant has become apparent. Although not an approved anticoagulant for PPI, unfractionated heparin (UFH) has historically been the procedural anticoagulant of choice, based primarily on its traditional use during percutaneous coronary interventions (PCIs). However, the widely accepted limitations of UFH have resulted in a search for a better treatment. The direct thrombin inhibitor bivalirudin (Angiomax, The Medicines Company, Parsippany, NJ) fills the void created by limitations of other available agents, and provides a safe alternative for use during PPI, as demonstrated in the recently completed APPROVE Trial.

PERIPHERAL ARTERIAL DISEASE

Peripheral arterial disease (PAD) is one of the major manifestations of systemic atherosclerosis and affects approximately 10 million to 14 million Americans each year. Because the disease is initially asymptomatic, it is underdiagnosed and undertreated.[1] With progression of the disease, symptoms will emerge, and if left untreated, it can lead to organ deterioration, severe chronic leg ischemia, and ultimately limb loss. A treatment strategy involving PPIs is well suited for patients with PAD who have increased comorbidities and risk characteristics compared to patients with isolated coronary artery disease.[2]

The risks and long-term efficacy of PPIs, however, remain incompletely defined largely because of the heterogeneity of patient populations in published studies and the variability of reporting methods and defining endpoints. In general, the small number of existing reports suggests that PPI outcomes show worse acute and long-term outcomes compared to PCI results. This is not unexpected given that PPIs require larger sheath sizes and longer procedural duration times, which are factors predictive of ischemic and hemorrhagic complications.[3]

The poor outcomes seen in PPI compared to PCI are also likely related to the high prevalence of comorbidities and risk factors in patients with PAD. Most patients with peripheral atherosclerosis also have concomitant coronary and carotid artery diseases, resulting in increased mortality and morbidity. Furthermore, the risk factors for the development of PAD, including hypertension, advanced age, smoking, diabetes, and impaired renal function, are indicators of complications during interventional procedures.[4-8]

The need for a procedural anticoagulant in PCI is well established. The similar etiology of PAD suggests that anticoagulation is a necessary component for patients undergoing PPI procedures. This need may be more vital during PPI, during which patients are at higher risk and there is, in general, a greater thrombus burden than would exist in the smaller coronary arteries and a higher incidence of both diabetes and chronic renal insufficiency.[5] Currently, there is no approved procedural anticoagulant for use during PPI, and consequentially, an anticoagulation strategy to enhance the safety and efficacy of the procedure is crucial.

UFH HEPARIN: ACCENTUATED SHORTCOMINGS?

As a result of its familiarity and historical use in PCI, anticoagulation with UFH has been extrapolated into the realm of PPI, despite its many well-documented limitations. There is no established dosing regimen for heparin, resulting in wide variability from patient to patient. UFH has been shown to stimulate both platelet activation and aggregation. UFH exhibits nonspecific protein binding, which reduces the amount of heparin available to exert an anticoagulant effect, and therefore requires frequent monitoring to ensure adequate anticoagulation. Treatment with UFH may result in antibodies that increase the risk of heparin-

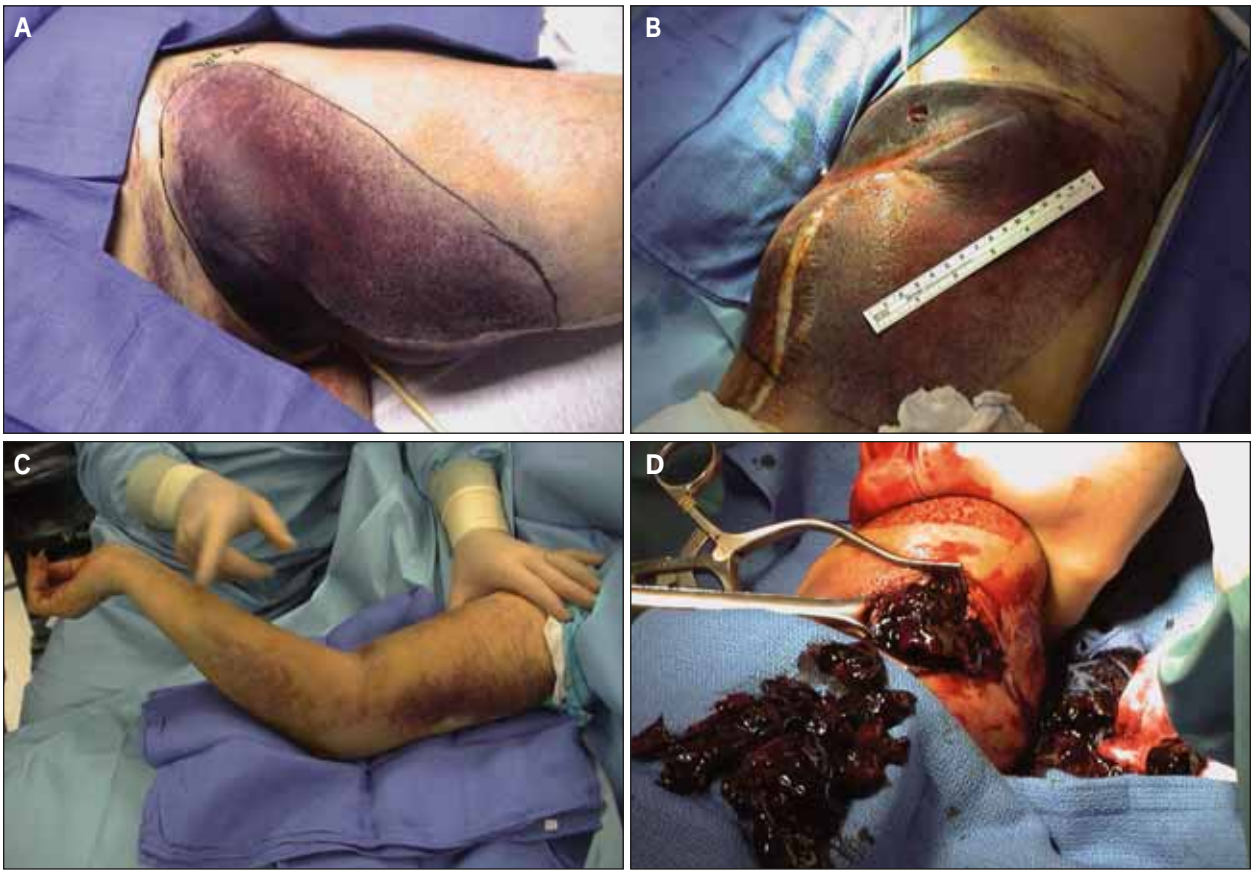

Figure 1. Large nonsurgical groin hematoma after cardiac catheterization (A). Large expanding groin hematoma requiring surgical repair (B). Late brachial artery bleed (1 week) after PCI presenting as a compartment syndrome requiring surgical treatment (C). Surgical evacuation of a hematoma in the same patient (D).

induced thrombocytopenia and thrombosis syndrome. The most significant limitation of UFH is its inability to inhibit clot-bound thrombin, leaving large amounts of active thrombin free to generate more thrombin and activate platelets.[9]

In PCI, heparin limitations resulted in the addition of adjunctive therapies such as glycoprotein (GP) IIb/IIIa inhibitors and thienopyridines, reducing ischemic events but increasing the risk of bleeding (Figure 1). This risk may be more amplified in PPI patients than those undergoing PCI for several reasons. First, recent data suggest that patients with PAD are at greater risk for thromboembolic complications due to increased levels of fibrinogen and von Willibrand factor compared to healthy subjects.[10-12] Fibrinogen promotes thrombosis through platelet aggregability, and von Willibrand factor stimulates thrombin generation and is crucial for both platelet adhesion and aggregation, increasing the risk of thrombotic events.[13,14] Second, data have verified that patients with PAD exhibit a hypersensitive response to heparin, and thereby may be at elevated risk for developing heparin-induced thrombocytopenia and thrombosis syndrome.[10] Finally, patients with peripheral atherosclerosis have shown increased platelet activity, and it has been postulated that platelet activation by heparin may explain the increased rate of stent thrombosis in patients treated with anticoagulant therapy.[15]

UNIQUE MECHANISM OF ACTION AND OUTCOMES IN PCI AND PPI

Bivalirudin, a thrombin-specific anticoagulant approved for use in PCI, overcomes many heparin limitations and may prove to be a superior anticoagulant in PPI as well. The dosing of bivalirudin is fixed and linear, thus frequent monitoring is unnecessary. Bivalirudin's direct and reversible thrombin-specific binding ensures 100% bioavailability and rapid return to hemostasis. It is able to inhibit both soluble and clot-bound thrombin, thereby inhibiting thrombin-mediated platelet activation and further thrombin generation. Finally, bivalirudin does not cross-react with heparin PF4 antibodies and has low immunogenic potential.[16] These

properties provide potential benefits over UFH during PPI in which thrombin activation is expected to be significant given the extent of atherosclerotic burden.[5]

These characteristics provide some explanation for the unique observation of reduction in both ischemic and bleeding complications in PCI. In more than 10 percutaneous transluminal coronary angioplasty and PCI trials, bivalirudin provides a net benefit superior to similar agents. An analysis of more than 6,000 patients found that compared to heparin, bivalirudin reduced the triple endpoint of death, myocardial infarction (MI), and revascularization by 24% (5.7% vs 7.5%; *P*=.0035) and reduced hemorrhage by 63% (*P*<.0001)[17] (Table 1). Evidence of bivalirudin benefit in high-risk patients was first demonstrated in the Bivalirudin Angioplasty Trial (BAT).[18] In a defined cohort of post-MI patients, treatment with bivalirudin resulted in lower incidence of death (0% vs 0.5%), MI (3% vs 5.6%), and revascularization (3% vs 6.2%) when compared to heparin. These outcomes are further supported by the 1-year mortality data in the REPLACE-2 Trial, which showed nonsignificant trends toward lower 1-year mortality with bivalirudin in all patient subgroups, with the greatest benefit among patients at higher risk for death.[19] These data provide the background and rationale for bivalirudin use in PPI.

THE APPROVAL TRIAL

The largest PPI trial with bivalirudin (to date) is the Angiomax Peripheral Procedure Registry of Vascular Events (APPROVE) Trial. APPROVE was a multicenter, prospective study that assessed the safety of replacing heparin with bivalirudin in patients undergoing PPI of the renal, iliac, or femoral arteries.[20] Patients were treated with bivalirudin as the sole procedural anticoagulant, with GP IIb/IIIa inhibitors used at the investigators' discretion. The primary endpoint was procedural success defined as residual stenosis ≤20%. Secondary endpoints included activated clotting time (ACT) values, ischemic and bleeding complications, as well as times to sheath removal, ambulation, and discharge. Bivalirudin was administered as a 0.75-mg/kg bolus followed by a 1.75-mg/kg per hour intravenous infusion for the duration of the procedure.

Aspirin and clopidogrel were administered to 96.8% and 95% of patients, respectively. GP IIb/IIIa inhibitors were used in 4.4%. Procedural success was achieved in 95% of patients overall; 97.1% of patients in the renal group, 93.5% of the iliac group, and 94% of the femoral group. ACT measurements were consistent among treatment groups. Mean ACT values 5 minutes after bolus injection were: renal, 353.85; iliac, 335.95; femoral, 343.53 seconds. An ACT level of >250 sec was achieved in 95.8% of patients 5 minutes after bolus injection and maintained until the end of the procedure in 92.7% of patients, demonstrating consistent anticoagulation.

Event rates at discharge and 30 days were low and comparable between groups (Table 2). There were no deaths and one MI (0.2%) through day 30. Unplanned revascularization was performed in four instances (0.8%) and amputation occurred in two patients (0.4%) by 30 days. Bleeding events also were low. Overall, protocol-defined major and minor hemorrhage occurred in 2.2% and 8.5% of patients, respectively. Rates of TIMI major and minor hemorrhage were 0.4% and 2%, respectively.

Other smaller registries report outcomes consistent with those of the APPROVE Trial. Knopf et al administered bivalirudin to 72 patients undergoing peripheral interventions; there were no reports of major bleeding, death, or stroke, and procedural success was achieved in 100% of cases.[21] Allie et al have shown 100% procedural success, with no major complications in a series of 175 renal and 75 iliac patients treated with bivalirudin.[3] A study by Shammas et al[22] resulted in an overall complication rate of 4.2% with bivalirudin (n=48). An event rate of 9.2% for patients treated with UFH during PPI had previously been reported by

TABLE 1. CLINICAL OUTCOMES WITH BIVALIRUDIN COMPARED TO HEPARIN IN 10 POOLED PCI TRIALS (N=6,134)

Outcomes	Bivalirudin (N=3,277)		Heparin (N=2,857)		*P* Value
	n	%	n	%	
Any event	241	7.4	372	13	<.0001
Death/MI/TVR	186	5.7	215	7.5	.003
Death/MI	113	3.4	127	4.4	.045
Death	7	0.2	8	0.3	.599
MI	109	3.3	124	4.3	.038
TVR	107	3.3	137	4.8	.002
Hemorrhage	91	2.8	217	7.6	<.0001

TVR = target vessel revascularization.

TABLE 2. CLINICAL OUTCOMES FROM THE APPROVE TRIAL AT 30 DAYS

Outcomes	Renal (N=173)		Iliac (N=140)		Femoral (N=184)		EPP* (N=505)	
	n	%	n	%	n	%	n	%)
Procedural success	168	97.1	130	93.5	172	94	475	94.8
Death	0	0	0	0	0	0	0	0
MI	0	0	0	0	1	0.5	1	0.2
Unplanned revascularization/ surgical intervention	0	0	0	0	4	2.2	4	0.8
Amputation	0	0	0	0	2	1.1	2	0.4
Major bleeding protocol defined†	4	2.3	4	2.9	3	1.6	11	2.2
Minor bleeding protocol defined†	10	5.8	14	10	19	10.3	43	8.5
TIMI major hemorrhage†	0	0	1	0.7	1	0.6	2	0.4
TIMI minor hemorrhage†	2	1.2	4	2.9	4	2.2	10	2.0

**Evaluable patient population.*

†Hemorrhage by discharge.

the same group. The complication rate appeared to double with UFH when compared to bivalirudin.[5] Another study of 69 interventions demonstrated adequate anticoagulation with bivalirudin, with no adverse events such as bleeding, acute thrombosis, death, or development of heparin-induced thrombocytopenia and thrombosis syndrome.[23]

These outcomes appear to compare favorably with the Shammas heparin registry[24] and with a recently published analysis of more than 7,000 patients.[5,24] This pooled analysis of 39 publications sought to define the various complication rates during PPI with UFH as the primary anticoagulant. The overall success rate was 89.2%, and complication rates were: death (1.6%), major bleeding (2.1%), MI (0.7%), and limb loss (1.9%). The authors concluded that complication rates remain high with the use of UFH, and that an aggressive search for a new anticoagulant is needed. The outcomes of trials with bivalirudin in PPI demonstrate that it is safe and effective, and suggest that it may be an attractive alternative to UFH.

CONCLUSION

Selecting an optimal antithrombotic therapy is vital to any peripheral vascular intervention. Clinical trial data demonstrate a net clinical benefit of bivalirudin in the contemporary PCI setting and suggest that these benefits may be extended to PPI. The PVD patient is likely at greater risk for both ischemic and bleeding complications during intervention, therefore outcomes should be improved with an optimal anticoagulation strategy. The results of the APPROVE Trial significantly increase the growing body of evidence that bivalirudin provides reliable and consistent anticoagulation regardless of the vessel being treated. ■

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