The use of endovascular therapy for obstructive lower extremity peripheral artery disease (PAD) has grown dramatically during the past 2 decades. Vascular specialists from a variety of backgrounds—surgical, medical, radiological, and other—converge on the treatment of these patients with PAD, each bringing unique technical, cognitive, and clinical insights from their respective fields of expertise. As interventional cardiologists have increasingly engaged in peripheral vascular intervention (PVI), they too have imported strategies and insights from a wealth of experience in percutaneous coronary intervention (PCI) to PVI. Chief among such insights is the desire to optimize periprocedural anticoagulation, minimizing procedure-related thrombosis and bleeding, which characterize the routine use of unfractionated heparin (UFH).

Bivalirudin has natural appeal for PVI because comparative studies in PCI demonstrated reduction in clinically significant bleeding with bivalirudin compared with UFH glycoprotein IIb/IIIa inhibitor (GPI) therapy. Although bivalirudin has been studied extensively in PCI, far less evidence exists for its potential advantage in PVI. Small studies suggest that bivalirudin may be safely and effectively used in renal and iliac artery interventions, but larger, randomized controlled trials are needed to compare its utility with UFH. Although bivalirudin with GPI was shown to be safe in PVI for critical limb ischemia (CLI), no statistical advantage was found compared with UFH. Fortunately, the large randomized controlled Endovascular Interventions With AngioMAX (ENDOMAX, ClinicalTrials.gov number NCT01913483) clinical trial comparing bivalirudin versus UFH in PVI in ≈4000 patients has completed enrollment, with results anticipated in the next year.

At present, UFH represents the dominant anticoagulant strategy in PVI. The relatively higher cost of bivalirudin—even in generic formulation because of expiration of the US patent—may impede its broader adoption in PVI. In addition, because revascularization of chronic total occlusions is common in PVI, the lack of reversibility of bivalirudin may reduce its desirability in cases with potential for vascular perforation. Still, there remains great interest to use bivalirudin for PVI, prioritizing its rapid onset of therapeutic anticoagulation, reliable pharmacokinetics, and rapid offset of anticoagulation.

In this issue of Circulation: Cardiovascular Interventions, Kimmelstiel et al compare the clinical outcomes of patients undergoing PVI with bivalirudin or UFH alone in a retrospective, propensity-matched assessment. The investigators included patient outcomes from the Premier hospital database, which provides patient-level data from >600 hospitals in the United States. Adults aged ≥18 years who underwent PVI of the lower extremities—defined as the iliac bifurcation or lower—between 2008 and 2012 were identified using International Classification of Diseases Ninth Revision codes. Patient demographics and clinical severity of PAD were identified through database review, as well as medications administered 1 day before on the day of PVI and 1 day after. Finally, the clinical specialty of the interventional physician (cardiology versus noncardiology, ie, radiology or vascular surgery) was also evaluated. The anticoagulant strategy used during PVI was abstracted from hospital billing data; patients who received GPIs during treatment were excluded from the analysis. Five individual end points were examined: (1) mortality, (2) myocardial infarction, (3) stroke, (4) lower extremity amputation on the day of or after PVI, and (5) transfusion. In addition, 2 composite end points were evaluated: major adverse clinical events (death, myocardial infarction, stroke, or amputation) or net adverse clinical events (death, myocardial infarction, stroke, amputation, or transfusion). Because of the retrospective nature of this study, propensity matching was then performed to match each bivalirudin-treated patient with a comparable UFH-treated patient.

In the final assessment, 23,934 patients were analyzed of whom 4370 received bivalirudin (18%) and 19,564 received UFH (82%). Of note, those receiving bivalirudin were more often older, nonwhites, and men, with a greater burden of cardiovascular risk factors and previous symptomatic coronary artery disease requiring PCI or coronary artery bypass grafting than those who were treated with UFH. Conversely, UFH was more frequently used in patients with CLI and was more likely to be used by noncardiologists. These differences were largely mitigated by propensity matching. The final analysis included 7298 subjects, in whom PVI performed with bivalirudin resulted in statistically lower mortality (0.3% versus 0.7%; P = 0.017), transfusion (4.0% versus 5.3%; P = 0.009), major adverse clinical events (2.3% versus 3.5%; P = 0.003), and net adverse clinical events (5.9% versus 7.9%; P < 0.001) compared with those treated.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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Circ Cardiovasc Interv is available at http://circinterventions.ahajournals.org
DOI: 10.1161/CIRCINTERVENTIONS.115.003424

Will Bivalirudin Have an Impact in Peripheral Vascular Interventions?

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with UFH. In addition, there was a trend toward fewer minor amputations in the bivalirudin group (1.5% versus 2.0%; \(P=0.093\)), which reached statistical significance after logistic regression analysis (\(P=0.006\)) rather than with propensity matching. These results withstood sensitivity analysis that included patients who received GPI (454 in the UFH group and 194 in the bivalirudin group). Notably, subgroup analyses suggested that reductions in major adverse clinical events were more likely in bivalirudin patients who were men, diabetics, did not have chronic heart failure or anemia, did have CLI or target lesions in the iliacs, had ather- 

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mendications may have effect on the therapeutic efficacy of bivalirudin in PVI. This concern may be supported by the unanticipated finding in this study that patients receiving endovascular stents had an attenuated benefit from bivalirudin. Although acute and subacute stent thrombosis is rare after PVI, it remains unclear whether the use of bivalirudin may be associated with higher acute stent thrombosis risk in PVI as has been observed after PCI.4,12,13 Moreover, with the expansion of endovascular drug delivery technologies in PVI in the form of paclitaxel-coated balloons and nonpolymeric paclitaxel-eluting stents, rates of target lesion site thrombosis may increase independent from the periprocedural anticoagulant because of the prothrombotic nature of antirestenosis pharmacology and will need to be controlled for in future analyses.

Although the authors are to be congratulated on the implementation of this analysis, the societal implications and cost-effectiveness of use of bivalirudin in PVI remain to be determined. Armed with information from cost-effectiveness analysis, as well as prospective bleeding risk assessment as with the HAS-BLED (a composite score that predicts bleeding in patients with atrial fibrillation on oral anticoagulation with the following risk factors: hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly [>65 years], drugs/alcohol concomitantly) or the dual antiplatelet therapy score calculators, future anticoagulant and antiplatelet strategies may one day be tailored to each individual patient undergoing PVI.14,15 Although many questions remain about optimal strategies for patients undergoing PVI, the study by Kimmelstiel et al16 provides new insight and motivation for further investigation into the role of bivalirudin in PVI, particularly in patients with high risk of bleeding.

Disclosures

Dr Parikh is a consultant for Abbott Vascular, Medtronic and member of Speakers Bureau for Abbott Vascular, Boston Scientific, Medtronic,
Spectranetics, and Astra Zeneca and received research grant support from Lutonix/CR Bard, Medtronic, Abbott Vascular, and Boston Scientific. Dr Drachman is a consultant for Abbott Vascular, St. Jude Medical, and Corindus Inc and received research grant support from Atrium Medical/Maquet and Lutonix/CR Bard.

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References

Key Words: Editorials • bivalirudin • hemorrhage • percutaneous coronary intervention • peripheral arterial disease
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doi: 10.1161/CIRCINTERVENTIONS.115.003424
Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-7640. Online ISSN: 1941-7632

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circinterventions.ahajournals.org/content/9/1/e003424

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