Will Bivalirudin Have an Impact in Peripheral Vascular Interventions?

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The use of endovascular therapy for obstructive lower extremity peripheral artery disease (PAD) has grown dramatically during the past 2 decades.1 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.1 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 plus glycoprotein IIb/IIa inhibitor (GPI) therapy.2–4 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.5 Although bivalirudin with GPI was shown to be safe in PVI for critical limb ischemia (CLI), no statistical advantage was found compared with UFH.6 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 al7 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.
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 atherectomy performed, did not have implantation of stents, and had procedures performed by cardiologists rather than noncardiologists.

This study represents the largest patient population analyzed to date comparing bivalirudin with UFH in PVI. The primary differences in outcomes noted in this study are related to the significant reduction in bleeding associated with bivalirudin, mirroring findings in previous studies in PCI both with and without adjunctive use of GPI. We agree with the authors’ postulate that reduction in bleeding may well explain the differences in mortality and major adverse clinical events observed because excess bleeding has consistently been demonstrated to increase mortality hazard in other data sets.\(^5\)\(^-\)\(^11\) In this analysis, the addition of GPI was infrequent and did not affect the overall study outcome, further strengthening the hypothesis that bivalirudin reduces significant bleeding in PVI. It is worth noting that, although the arterial access site was not evaluated in this study, the vast majority of PVI procedures involving lower extremity PAD are performed via transfemoral access. It remains speculative whether alternative arterial access (such as transradial or transpedal) affects procedurally related bleeding or need for transfusion and could, therefore, influence the outcomes reported in this assessment. In addition, the reduction in amputation rates after PVI in patients treated with bivalirudin have not previously been observed. This finding warrants further investigation. In real-world treatment of patients with CLI, clinical goals frequently incorporate minor amputation as part of a successful limb salvage strategy. As such, a more thorough understanding of the goals of treatment in which amputation is performed must be incorporated into the adjudication of amputation as an adverse event. It remains unclear if the amputations observed in this study were unplanned or planned or if the anticipation of amputation might have influenced the operators’ perspective on desired anticoagulant strategy. Ultimately, the role of bivalirudin in reducing risk of amputation in PVI may be best adjudicated through prospective, randomized controlled evaluation.

Although the authors acknowledge the limitations of their retrospective analysis, given the current absence of large randomized controlled clinical trials, their study represents the best available knowledge comparing bivalirudin with UFH in PVI. The forthcoming ENDOMAX trial will provide greater insight into patient-level rates of complications with PVI using bivalirudin or UFH, especially bleeding rather than transfusion as a surrogate for bleeding. In addition, perhaps the ENDOMAX data will provide additional insight into the discrepancy in unplanned amputation observed in this study with each of the 2 anticoagulant strategies.

The methodology of this study may not account for several potential confounding variables. First, although the use of direct thrombin inhibitor therapy is inherently desirable in endovascular intervention, more recent data in PCI suggest a far more attenuated advantage of bivalirudin compared with UFH when considering the spectrum of clinical manifestations of coronary atherothrombosis.\(^12\)\(^,\)\(^13\) In addition, the bleeding hazard may vary along the spectrum of clinical presentation in patients with PAD and are potentially even more dramatically different considering—for example—the bleeding risk of a patient with claudication compared with one who presents with CLI. As a result, the combining of a spectrum of clinical presentations in a single analysis may obscure the nuance of potential subgroups in whom bivalirudin may offer particular advantage. Second, important differences in antiplatelet therapy were not evaluated in this study. Although practices vary, many patients with documented PAD still do not receive guideline-directed medical therapy and are not taking aspirin alone. In addition, perhaps the background therapy with antiplatelet medications 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 PCI, \(^14\)\(^,\)\(^15\) although the use of bivalirudin may be associated with higher acute stent thrombosis risk after PCI as has been observed after PCI.\(^14\)\(^,\)\(^15\)\(^,\)\(^16\) 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 al\(^17\) 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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doi: 10.1161/CIRCINTERVENTIONS.115.003424

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