Antiplatelet Therapy for Peripheral Artery Disease: An Interview With Larry Diaz-Sandoval, MD

Interview by Jennifer Ford

**VDM:** What is the state of peripheral arterial disease (PAD) and critical limb ischemia (CLI) in the US population?

**Diaz:** Critical limb ischemia represents the terminal stage of PAD and occurs when inadequate perfusion of the capillary beds renders tissues unable to sustain their viability. It is defined by the presence of rest pain and/or tissue loss for at least 2 to 4 weeks that can conclusively be attributed to occlusive arterial disease. The diagnosis is clinical in nature, where patients have symptoms in Rutherford Becker class IV, V, and VI. The European Consensus Conference has also included the need for analgesia for more than 2 weeks or ischemic tissue loss with an ankle pressure of less than 50 mmHg as part of the definition. Anatomically, CLI is characterized by multilevel and multivessel infrainguinal and tibial-pedal arterial stenoses and occlusions that create a severe imbalance between supply and demand of oxygen in the affected tissues, compromising their viability and threatening limb loss. It is estimated that 1.5 million subjects in Europe and 2 million in the United States over age 50 manifest symptoms of CLI. One-year mortality and major amputation rates range from 20% to 50%. It occurs in approximately 1% to 3% of all PAD cases with an incidence between 500 and 1,000 persons per million per year in Europe and the United States.

**VDM:** How has your practice changed in recent years regarding PAD and CLI diagnosis and treatment?

**Diaz:** We have become more aggressive at trying to identify as early as possible those patients that present with advanced PAD (Rutherford III) and CLI symptoms. In our experience, we have noticed that patients with claudication may have anatomic features characteristic of patients with CLI and that there is more of a continuum of symptoms and anatomic features than a rigid, “clear-cut” separation of symptoms that correlate in linear fashion with specific phenotypes. It is therefore important to be aware of this reality to diagnose patients at the earliest possible stages and implement medical therapies that address the multitude of risk factors that increase the risk of progression of disease such as...
hypertension, hyperlipidemia, diabetes, and tobacco use. In terms of revascularization, the evolution of technologies has led to the use of endovascular revascularization as the primary strategy for patients with PAD and CLI, with use of ultrasound guidance and retrograde tibial pedal access as some of the newest additions to the interventionalist’s toolbox.

**VDM:** Can you outline or comment on your institution’s protocol for patients presenting with PAD and CLI?

**Diaz:** Over the years we have developed iterations of this protocol to address the management of patients with PAD who present at different stages, from minimal symptoms, to life-limiting claudication, to the terminal stage represented by those patients with CLI. When patients are referred due to abnormal pulse findings, or symptoms of claudication, we see them at the next available opportunity (within 2 weeks maximum). Patients undergo a detailed history and physical exam with bedside Doppler evaluation in the office and are scheduled to undergo noninvasive testing (ABI, duplex ultrasound) with a follow-up visit within 4 weeks. If they have rest pain or tissue loss, they are typically worked into the schedule within 24 hours, undergo their examination, Doppler evaluation and/or duplex ultrasound mapping within 24-48 hours and are scheduled for selective angiography and intervention as soon as possible. We have developed a CLI team, and when a CLI patient undergoes intervention and is admitted to the hospital, the podiatrist, orthopedist, infectious disease specialist, and wound care specialist are involved from the beginning, in order to provide the comprehensive care necessary to obtain the best outcomes for these patients.

**VDM:** What concerns do you have that are specific to treating diabetic patients, who comprise a large portion of PAD (>50%-60%) and CLI patients (80%)?

**Diaz:** Patients with long-standing diabetes mellitus typically have not only PAD (regardless of the stage), but also advanced kidney disease, which places them at increased risk of contrast-induced nephropathy after traditional contrast-guided endovascular interventions. Also, the combination of these two processes increases the deposition of calcium along the medial layer of the lower extremity arterial tree, creating an element of the CLI plaque that makes revascularization procedures more challenging. In patients with diabetes, the risk of PAD is 3- to 4-fold higher and it tends to be more aggressive than in patients without diabetes, with a major amputation rate 5 times to 10 times higher. Typical infrapopliteal (IP) diabetic disease is characterized by long, multilevel disease involving all three IP vessels. Isolated IP disease is mainly seen in the elderly (>80 years old), diabetic, or dialysis-dependent patients. These patients have higher risk for amputation and shorter amputation-free survival compared to those with combined femoropopliteal and IP disease.

**VDM:** The 2011 ACCF/AHA guidelines provide a Class I recommendation, Level of
Evidence A, for antiplatelet therapy in individuals with symptomatic atherosclerotic lower-extremity PAD. Can you comment on the importance of having a strong antiplatelet agent on board during peripheral vascular interventions?

Diaz: The recommendation is to reduce the risk of MI, stroke, and vascular death in patients with symptomatic atherosclerotic lower extremity PAD, prior to either revascularization (endovascular or surgical) or amputation. Aspirin and clopidogrel are the agents addressed in this iteration of the guidelines, and both received a Class I recommendation with Level of Evidence B for this purpose. Warfarin, on the other hand, received a class III recommendation (no benefit) in the absence of any other proven indication for its use. It should not be added to antiplatelet therapy to reduce the risk of ischemic events in patients with lower-extremity PAD. The guidelines did not address the use of antiplatelets during peripheral interventions.

VDM: What is in your pharmacological toolkit with regards to anticoagulant and antiplatelet therapy in PAD/CLI, both in above-the-knee and below-the-knee cases?

Diaz: Patients undergoing endovascular interventions for symptomatic lower-extremity atherosclerotic PAD and/or CLI are typically pretreated with dual antiplatelet therapy, using aspirin and a P2Y12 receptor antagonist (Plavix, Brilliinta, Effient). During the intervention, intravenous heparin is typically utilized, although bivalirudin and argatroban have been reported to be efficient under specific circumstances. When using heparin, it is important to dose it appropriately in order to obtain activated clotting times of >200 seconds when performing above the knee interventions or >250 seconds when performing below-the-knee interventions.

VDM: In which cases would you use a glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitor? Which GP IIb/IIIa inhibitor have you selected and why? What dosing strategy do you use in the peripheral setting?

Diaz: I have used GP IIb/IIIa inhibitors in selected peripheral interventions. I have had patients who could not (at the time of their emergent intervention) take oral P2Y12 platelet receptor antagonists for different reasons (for example, small bowel obstruction, intubated patients, patients with ileostomies). I have also used it in patients with burden, slow flow, or postinterventional residual thrombus. At our institution, eptifibatide used to be the agent of choice, however tirofiban has replaced it because it offers a similar efficacy and safety profile, while being significantly cheaper. When we use it, we use the same regime that is recommended for patients undergoing coronary interventions.

Interestingly enough, the largest data set on the use of GP IIb/IIIa inhibitors during lower-extremity endovascular interventions has just been published in *Catheterization & Cardiovascular Interventions* online ahead of print in February of this year. The authors obtained data from the Nationwide Inpatient

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Sample database from 2006 to 2011, on more than 90,000 patients. Multivariate analysis revealed that GP IIb/IIIa inhibitors were used in less than 2% of peripheral endovascular interventions and were associated with a significantly lower rate of amputations. However, it also showed an association with increased incidence of the composite endpoint of post-procedural complications and in-hospital mortality, as well as increased hospitalization costs. The authors did acknowledge that further appraisal of the use of GP IIb/IIIa inhibitors in peripheral interventions is warranted via performance of randomized trials because this database analysis has several limitations (specifically related to the lack of indications that led to their use in the almost 2,000 patients that received the active treatment). Another limitation is that the agents and dosing regimes utilized were not specifically addressed.

**VDM:** Is there a concern for risk of stent thrombosis in PAD patients? If yes, how do you recommend adjusting pharmacotherapy to prevent it, and does a GP IIb/IIIa inhibitor, like tirofiban HCl, play a significant role in it?

**Diaz:** Whenever a stent is implanted in any arterial bed, there is a risk for stent thrombosis. The risk of stent thrombosis has been linked to several mechanical and technical aspects related to the intervention such as stent strut apposition, adequate stent sizing, presence and severity of underlying calcification, need to overlap stents and the length of said overlap, length and diameter of the stented segment, as well as the presence of thrombus during stent implantation. There are also patient-related factors such as thrombophilias and other comorbidities (such as diabetes, renal disease, concomitant tobacco use), quality and number of patent outflow vessels, compliance with medical therapy, and so on.

Of late, Plavix is the most commonly used P2Y12 receptor antagonist due to its availability as a generic medication. This is typically used in conjunction with aspirin. We do see (not uncommonly) that patients present with stent thrombosis despite compliance with the dual antiplatelet regime, and in these instances the suspicion is that the patient may be resistant to clopidogrel, and therefore we commonly proceed to change the P2Y12 receptor antagonist. In the acute setting, the use of intravenous GP IIb/IIIa inhibitors may be justified in patients unable to take oral medications, or in patients with evidence of slow flow, significant thrombus burden, poor run-off, and need for bailout stenting. As with all medications that are used in these scenarios, the risk of bleeding needs to be weighed against the risk of thrombosis. The use of GP IIb/IIIa inhibitors such as tirofiban HCl in these scenarios can prove useful due to the short half-life, providing reliable antiplatelet therapeutic effect and a favorable safety profile, as it can be shut off in the event of bleeding complications.

**VDM:** What are your preferred access routes for peripheral interventions? What would be the benefit of using alternative routes?

**Diaz:** The arterial access site for peripheral interventions varies per case. The most commonly
used is the retrograde contralateral common femoral with an “up and over” approach, as most operators are familiar and comfortable with this technique. However, this approach has several shortcomings when trying to cross long complex chronic total occlusions (CTOs), as it limits the ability to push crossing devices, to torque catheters and wires, and to deliver therapy. For these cases, we typically use the ipsilateral antegrade common femoral access, and not uncommonly (about 33% of the time) in combination with retrograde tibial-pedal access or retrograde distal superficial femoral artery access, as many of these complex CTOs do not allow for complete crossing when approached in an antegrade fashion. Radial and/or brachial arterial access is also utilized in selected cases when femoral access is not an option.

**VDM:** Your institution is currently enrolling subjects in the PRIME registry. What can you tell us about this registry and its progress? Is there a goal in the registry to examine the clinical and safety outcome of patients administered pharmacotherapy, specifically antiplatelet regimens such as GP IIb/IIIa inhibitors?

**Diaz:** PRIME is the first registry of its kind that attempts to elucidate the best diagnostic and endovascular therapeutic modalities for advanced PAD (APAD) and CLI. PRIME explores all aspects of APAD and CLI care, including the collection of comprehensive clinical, diagnostic, procedural, and follow-up data for 3 years following an index endovascular procedure. Analysis of this prospective, observational, multicenter registry will allow us to describe the clinical epidemiology, natural history, and the best diagnostic/endovascular therapeutic approaches for patients with APAD and CLI. Information collected includes demographics, medical history, previous vascular procedures, presenting symptoms, medications (including oral and intravenous antiplatelets and anticoagulants used in the pre, intra, and post-procedural periods), noninvasive testing, endovascular procedural modalities and details, and immediate outcomes (complications, symptom resolution, and technical success). Follow-up data is gathered at 30 days and 3, 6, 12, 24, and 36 months. From January 2013 to November 2015, 506 subjects underwent 833 endovascular revascularizations procedures to treat 1,182 target lesions. 30-day follow-up data has been collected on 424 (83.8%) subjects and 259 (51.2%) have already completed the 12-month follow-up.

**VDM:** In your opinion, what is most rewarding and challenging in treating PAD?

**Diaz:** The most rewarding aspect of treating patients with PAD and CLI is the near-immediate results. The patients and families typically notice a significant improvement in their symptoms and in their ability to perform activities as simple as walking without limitations, which they previously could not do because of the hemodynamic obstruction to their lower extremities. Having said that, the most challenging aspects are the difficulty that currently exists in identifying these patients at an earlier point
in their disease process, which would likely greatly simplify the treatment options and likely improve their prognosis (especially among patients with CLI). Another challenging aspect is the numerous comorbidities they typically have and the difficulty that most of these patients face when they are told they need to stop smoking.

Editor’s note: Dr. Diaz reports consultancy to CSI and Terumo, and payments for educational presentations from Terumo.

REFERENCES