

## Letters to the Editor

### Drug-eluting Balloons: Are These Failed Solutions for the Treatment of Below-the-knee Peripheral Artery Disease?

To the Editor:

It remains concerning that below-the-knee (BTK) peripheral artery disease (PAD), the clinical condition that most frequently results in lower limb amputation, still represents the greatest challenge for optimal and effective endovascular treatment.

Despite the evidence demonstrating an impressive reduction in major limb amputations from 40% to nearly 2%<sup>1,2</sup> among patients with critical limb ischemia (CLI) with the use of percutaneous transluminal angioplasty (PTA), new techniques and approaches are continuously evaluated.

Science continually strives for improvement in treatment; however, occasionally, these attempts offer modest improvement with a potential increase in risk. Such appears to be the case with the recent discontinuation of the IN.PACT DEEP below-knee trial in Europe using a drug-eluting balloon (DEB) catheter (Medtronic Vascular, Santa Rosa, CA). This and other similar devices have been approved for use in Europe and other countries since 2010. The announcement identified a potential safety signal with a trend toward an increased rate of major amputations in the DEB study arm, compared with the standard PTA control group.<sup>3,4</sup>

Despite a significant effort by many investigators and sponsors to identify a more effective endovascular strategy for infrapopliteal artery disease, little advances have actually occurred. In our opinion, the reason for these failures remains centered on the underlying metabolic disorder, diabetes mellitus. Diabetes results in greatest risk of non-traumatic amputation more than any other condition.

PAD in patients with diabetes mellitus represents a special pathologic condition largely ignored by most. The unique elements that differentiate PAD in diabetes from typical atherosclerosis are very frequently underappreciated.

Whereas, atherosclerosis is described as inflammatory fatty plaque formation, with focal, eccentric, subintimal calcification, PAD in diabetes, particularly within the infrapopliteal arteries, represents a degenerative, circumferential, arterial disorder with the unique absence of inflammatory cells.

This condition is largely different from typical atherosclerosis. There is an increased amount of connective tissue, such as fibronectin, collagen, and glycoproteins, as well as an increased amount of calcium in the medial arterial layer.

The classically described circumferential Mönckeberg's medial calcification, typically associated with absence of

macrophages and lipids, is common in diabetes-related BTK-PAD and occurs independently from atherosclerosis, implying different pathologic mechanisms, including the duration of diabetes.<sup>5-10</sup>

This constellation of findings, known as diabetic macroangiopathy, is present in most of the diabetic patients with PAD; yet it has been totally ignored by the current official Atherosclerotic Lesions Classification document.<sup>11</sup>

As these specific pathologic changes have rarely been described in coronary and carotid arteries, even in diabetic patients, they probably did not attract the attention of researchers.

Consequently, BTK-PAD in diabetes remains confused with atherosclerosis and has been treated as such.

The diffuse circumferential dense arterial thickening noted in lower limb arteries may play a major role in the elastic recoil phenomena, resulting in restenosis even with the use of DEB catheters.

Elastic recoil, particularly of the infrapopliteal arteries, has led to the development of high-pressure long balloons with the general acceptance of the need for prolonged balloon inflations as standard technique.<sup>12</sup>

Understanding the true reason for failure of PTA in infrapopliteal endovascular intervention may result in the future development of very long self-expanding drug-eluting stents (DES), bioresorbable stents, and combination therapies with DEB as a component to counteract this phenomena but unfortunately available technology has not yet clearly addressed to this purpose.

Additional concerns are related to potential high risk of thrombosis in case of long self-expanding DES implantation in BTK arteries because of the typically slow blood flow in this territory and the possible delayed or prevented endothelium coverage of the stent strut. Furthermore, experiences collected during the last decade, implanting self-expanding long nitinol bare-metal stents in BTK arteries have been generally disappointing, confining their usage in bailout conditions only.

A second aspect that is often minimized is the critical importance of foot care in patients undergoing limb salvage. The quality of such postprocedure foot care results in marked variability in outcomes.

In diabetic patients with CLI, the high risk of limb loss occurs frequently as a consequence of the superimposed infection underlying ischemia of the soft tissue, including bone involvement.

In this scenario, limb salvage is strictly influenced by the quality, timing, and appropriateness of foot care procedures including infection management (including abscess drainage), debridement, and so-called "minor amputations" including toe or transmetatarsal, Lisfranc's, and Syme's amputations.<sup>13</sup>