Grasping the Nettle and Femoral Artery Stenting
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When brushed against, needles on the leaves of nettles inject a noxious toxin into the skin. However, grasping the nettle firmly bends the needles away from the skin, rendering it less painful. The expression “to grasp the nettle” is to boldly confront an issue in order to seek its resolution. The advice warns us against half measures and is timely as we gather scientific evidence to assess the value of percutaneous (and surgical approaches) to treating peripheral artery disease (PAD).

Claudication Versus Critical Limb Ischemia
Claudication and critical limb ischemia are the 2 symptomatic manifestations of PAD. Although they share a common pathology (atherosclerosis) and a high risk of death from cardiovascular causes, their natural histories differ. Claudication impairs patient quality of life by causing painful cramps and dysfunction (eg, limping) while walking. Patients learn to avoid walking or to stop and rest when they claudicate until the discomfort eases. Over several years, symptoms may improve with collateral flow or metabolic adaptation in muscle.1 However, many patients experience a progressive decline in walking and subsequent quality of life and independence. Fortunately, claudication rarely progresses to critical limb ischemia and limb loss (<2% per year).2

On the other hand, critical limb ischemia is characterized by rest pain, nonhealing or poorly healing ulcers, or gangrene and more extensive tissue loss. Although this is a smaller group of symptomatic PAD, the immediate risks are to the limb, with subsequent loss of function and independence related to the level of amputation.3 Vascular bypass surgery offers a viable treatment for patients with critical limb ischemia, but traditional surgical practice limits bypass surgery to all but the most severe cases of claudication. This hesitancy is based on small, but definite perioperative risks of death and cardiovascular events,4 the long-term risks of graft failure, and improved endovascular options.

Bare-Metal Nitinol Stents for Femoral Disease
Endovascular therapies, and in particular self-expanding nitinol stents, are the disruptive technologies. They offer revascularization at a much lower periprocedural risk4 and are particularly attractive for patients with claudication and femoral artery disease. However, the lower periprocedural risk does not diminish the importance of assessing long-term durability in symptom relief and function.

Balloon angioplasty alone is an attractive option for short lesions, but longer lesions may require bailout stenting to avoid abrupt closure from unstable dissections or excessive arterial recoil. Thus, balloon angioplasty with bailout stenting is a worthy comparator for primary stenting with nitinol stents. Whether this endovascular standard offers greater benefits or risks than medical therapy is uncertain because randomized trials are lacking.

Primary stenting with self-expanding nitinol stents offers greater acute gains in lumen size and a more appealing angiographic appearance than balloon angioplasty. Although case series and single-arm studies suggested safe and efficacious short-term results with nitinol stents, randomized trials compared to balloon angioplasty and bailout stenting helped to define the real value of this technology. In the 2 published randomized trials, primary stenting offered greater efficacy for patency and function (walking distance) in longer lesions (mean length, 130 mm)5,6 but not for short lesions (mean length, ∼45 mm).7

However, in recent studies, bailout stenting in the angioplasty control group was considered a treatment (target vessel) failure. For example, in the RESILIENT trial (Randomized Study Comparing the Edwards Self-Expanding Lifestent versus Angioplasty Alone In LESions INVolving The SFA and/or Proximal Popliteal Artery) trial, 40% of subjects in the control arm received bailout stenting.8 As a result, the primary end point of freedom from target vessel revascularization strongly favored primary stenting (87% versus 45%). Yet, other secondary end points such as quality of life and walking distance assessed by questionnaire were similar.8

Although the purists would agree with this approach of comparing femoral stents to balloon angioplasty alone, this is inconsistent with the approach used to assess coronary stents. In the pivotal coronary stent trials, bailout stenting was considered an integral part of the angioplasty strategy and did not contribute to the primary end point.9,10 Furthermore, the pathologies leading to acute bailout stenting (flow-limiting dissection, abrupt closure, and excessive recoil) are quite different from the more important causes of long-term failure because of restenosis or thrombosis.

Drug-Eluting Femoral Stents
Symptom recurrence because of restenosis and stent thrombosis is the Achilles heel of stenting. Extension of the coronary stent experience supports enthusiasm for drug-eluting stents to prevent restenosis in femoral stenting.
However, the results from the early randomized trials were disappointing. In the SIROCCO (SIROlimus Coated Cordis S.M.A.R.T. Nitinol Self-expandable Stent for the Treatment of Obstructive Superficial Femoral Artery Disease) short-term success at 6 months was followed by no difference between drug-eluting and bare-metal stents in SIROCCO II over a longer time frame. Critics point out that the stent fracture rate was fairly high at 20% to 30%, implicating the stent rather than the concept of drug-eluting stents.

In this issue of Circulation: Cardiovascular Interventions, the Zilver PTX study by Dake et al evaluates a newer drug-eluting platform. The stent elutes paclitaxel from a polymer-free nitinol stent, and stent fracture at 12 months was much lower (0.9%) than that in SIROCCO. Laudably, the study attempted a randomized design, but the Food and Drug Administration panel that reviewed the trial interpreted bailout stenting as a failure of long-term patency on the grounds that there was no stent approved for this indication in the United States. As a further complication of the study design, patients requiring bailout stenting were randomly allocated to the drug-eluting or bare-metal stent. Because one half of the balloon angioplasty group required bailout stenting, one quarter of the control group had the intervention being tested. This design potentially dilutes any benefits (or risks) of the drug-eluting stent.

Like the RESILIENT study, this definition of the primary efficacy end point led to large differences in the 12-month patency rates between the groups (83% versus 33%) but with little difference in symptoms and walking impairment scores. The dichotomy between symptoms and patency in the Zilver PTX and RESILIENT studies weakens the validity of this definition as a primary outcome.

The primary safety end point of Zilver may provide a more realistic estimate of the clinical benefit of drug-eluting stents in the fairly short lesions they studied (mean length, ≈65 mm). Over the 12 months of the study, the angioplasty group (with 50% bailout stenting) had a reasonable clinical result (83% event-free survival). However, target vessel revascularization, which made up virtually all the events, was 7% to 8% lower in the drug-eluting stent group. This benefit seems modest, but could be greater because one quarter of the angioplasty group received drug-eluting stents. A clue to a larger difference lies in the absolute 17% lower target vessel revascularization with drug-eluting stents among the subgroup with bailout stenting that was randomized to each stent type.

Alternative trial designs include the single-arm study comparing new stents to historical rates of target vessel failure. For example, the recent STRIDES (Superficial Femoral Artery Treatment with Drug-Eluting Stents) study reported outcomes in a series of patients receiving an everolimus-eluting femoral stent. Stent restenosis increased from 6% at 6 months to 32% at 12 months, an uncertain result without a control group. Single-arm studies may be easier than randomized trials, but like the nettle, we are stung by less-informative results through a weaker design.

### A Need for Consensus on PAD End Points

What we need is a clear consensus on the important outcomes of randomized trials of PAD and a commitment to the randomized controlled design. Claudication is a disease manifest by loss of function and independence. As such, symptoms reflecting these patient-oriented components of disease should be primary efficacy outcomes. Examples include walking distances (maximum and pain free), 6-minute walk tests, and quality-of-life measures. Target vessel revascularization based on worsening symptoms with objective functional deterioration (eg, walking tests rather than imaging studies) and critical limb ischemia are important objective safety end points. For critical limb ischemia, amputation leading to loss of function is a key short-term end point. Independence and walking are less affected by loss of a few gangrenous toes or metatarsals compared with below- or above-knee amputations. Clinical follow-up beyond 12 months is crucial to evaluating long-term benefits and risks.

End points of patency or failed patency derived from duplex ultrasound or angiography may reflect restenosis pathology but are only surrogates for the patient-oriented end points. Although duplex ultrasound criteria for failed patency are common end points in femoral stent trials, their validity as indicators of symptoms or impending occlusion is controversial.

The experience of recent trials of femoral artery stenting suggests that we need to reconcile the confusion of trial design and end point assessment. Representatives of the invested societies (eg, American Heart Association, American College of Cardiology, Society for Vascular Medicine, Society for Vascular Surgery, Society for Vascular and Interventional Radiology of North America), the Food and Drug Administration, the Centers for Medicare & Medicaid Services, and industry should consider thrashing this out with one another to establish clear guidelines for informative trials.

### Clinical Practice

The decision to stent the femoral artery, particularly long lesions, is not one taken lightly. Both we and the patient are entering a long contract where surveillance by clinical assessment, functional tests, and imaging are required to identify symptom recurrence due to new disease and restenosis for repeat procedures before stent occlusion occurs. This model is analogous to regular surveillance of lower-extremity bypass grafts by vascular surgeons. Close assessment may provide sustained benefits, particularly in very-long femoral artery stenting, but the potential for drug-eluting stents and drug-coated balloons is intensely appealing and worthy of clinical trials with a strong design.

The long-term benefits of drug-eluting femoral stents remain uncertain. Our preconceptions based largely on the success of drug-eluting stents in the coronary arena should not prevent us from testing their effectiveness and long-term risks in the much larger and longer femoral artery. Our willingness to seek the truth depends on our ability to grasp the nettle by resisting our own preconceptions, coming to a consensus of which end points are important, and completing informative randomized trials.

### Disclosures

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