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EDITORIAL COMMENT

What's a Doctor to Do? Balloon, Stents, Drugs, Drills, and Treadmills

Are We Closer to the Optimal Algorithm?*

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On the one hand, we may all be enthusiastic. For decades, physicians, regulators, reimbursement policymakers, and patients have hoped that the level of evidence guiding the treatment of peripheral artery disease (PAD) would improve from single-center, retrospective, "this is how I do it" papers and prospective single-arm registries to randomized clinical trials. In fact, with the publication of the first randomized trial of drug-eluting stents for the treatment of femoropopliteal PAD, we welcomed a new era in technology and evidence (1). Although several critics wondered whether the conclusions drawn from the Zilver PTX (Zilver PTX Randomized Controlled Trial of Paclitaxel-Eluting Stents for Femoropopliteal Disease) study were relevant to modern clinical practice, because the comparator arm was percutaneous transluminal angioplasty, a treatment used with less frequency by interventionists, the Zilver PTX study raised the proverbial bar of evidence expected by interested parties.

Subsequently, a large-scale, prospective, multicenter randomized trial of a novel paclitaxel-coated angioplasty balloon catheter compared with an uncoated angioplasty catheter ushered in the era of non-stent-based drug-device combination products (2).

With this increase in levels of evidence, it appears that drug-device combination therapy has emerged as a major endovascular strategy for infrainguinal PAD. In this issue of *JACC: Cardiovascular Interventions*, a multicenter, prospective outcomes registry from well-respected investigators from Japan (the ZEPHYR study [Zilver PTX for the Femoral Artery and Proximal Popliteal Artery]) has added to our knowledge base, providing predictors of restenosis (3). Across multiple centers in Japan, 690 patients with intermittent claudication or critical limb ischemia were treated with the Zilver PTX stent (Cook Medical, Bloomington, Indiana). Investigators were encouraged to perform intravascular ultrasound (IVUS) assessment of the target lesion before and after intervention, and patients were followed with either angiography or noninvasive arterial duplex ultrasonography for 1 year following intervention. Perhaps

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of greatest importance of these data is the "real-world" nature of the patients enrolled in this multicenter registry. The mean lesion length in the Zilver PTX randomized trial ranged from 63.1 to 66.4 mm. In the current ZEPHYR study, the mean lesion length was 167 mm.

The restenosis rate with the Zilver PTX stent was 37% in this series, greater than the 16.9% restenosis rate of the Zilver PTX arm of the randomized trial. Of those patients who completed follow-up, lesion lengths longer than 160 mm and smaller diameters of the treated segments (as measured by IVUS) were predictors of restenosis. In fact, the primary patency

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of patients without predictors of restenosis was 85%, but if 2 or more risk factors were evident, the primary patency dropped to 49%.

Although these 2 results are quite different, one reason is self-evident: the patients in the ZEPHYR registry were more complex than those included in the randomized trial. Lesion lengths are longer, and one-third of patients presented with critical limb ischemia (CLI), whereas only 8.5% to 8.9% of patients in the randomized trial had CLI.

The major limitation of the ZEPHYR study includes the lack of a prospective comparator arm, preventing the ability to compare, head-to-head, the results of the randomized trial to this registry. Of similar importance, interpretation of the IVUS and follow-up duplex ultrasonography images were performed by the site investigators rather than having them interpreted by a central reading laboratory. In the recent Peripheral Academic Research Consortium (PARC) publication (4), broad representation by physician and regulatory experts from the United States and Japan clearly stated that independent adjudication of images be performed in clinical trials.

Given these data, combined with more recent data emerging about the treatment of symptomatic PAD, excitement must be tempered by the lack of comparative device data. Physicians managing patients with PAD have no reliable data demonstrating outcomes comparing a drug-eluting stent to a drug-coated balloon. With the ever-increasing interest in cost of care, we have no objective data supporting comparative effectiveness leading to appropriate decision making with modern medical devices. The limited cost-effectiveness data are largely modeled on the basis of previously published data with a series of "suppositions," falling short of allowing appropriate value-based decisions.

Comparisons of various endovascular devices, both to each other (5) and to surgery, specifically in patients with CLI (6), are emerging, but until we have the results, the pressure by hospital groups, purchasing agencies, payers, and regulators to decide what strategies are appropriate for patients represent real threats. It is the physician who possesses the experience, skill, and capabilities that are best suited to determine optimal treatment. Cost pressures muddy the waters of decision making, particularly without objective cost-effectiveness data, and economic models only carry the debate so far. In addition, the comparison of endovascular or surgical revascularization to exercise training, considered by some as the most cost-effective treatment, remains confusing. Recent publication of the CLEVER (Claudication: Exercise Versus Endoluminal Revascularization) trial 6-month data (7) suggested that supervised exercise therapy is more effective than endovascular revascularization for aortoiliac PAD. The 18-month data, however, demonstrate that any initial advantage of exercise therapy over stent revascularization is lost (8).

Until we have a series of high-quality comparative studies of different revascularization strategies for patients with PAD, the elusive algorithm of care will be relegated to opinion, conjecture, bias and margin pressures—none of which really help our patients. Adoption of the PARC (4) recommendations will at least set a common bar for the organization and implementation of these trials. Time is of the essence, as our patients with PAD continue to suffer and die (9).

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