Editorial

“POBA Plus”
Will the Balloon Regain Its Luster?

Timothy D. Henry, MD; Robert S. Schwartz, MD; Alan T. Hirsch, MD

Endovascular therapy of arterial occlusive disease has made impressive progress since the first balloon angioplasty conceived by Dr. Charles T. Dotter in 1964, followed by the first peripheral balloon angioplasty by Dr. Andreas Gruntzig in 1974. Each advancement has frequently faced skepticism after the initial clinical experience. Thankfully, skepticism was met in kind with research seeking facile, minimally invasive, durable, safe, and cost-effective arterial occlusive disease therapy. The result is an impressive and successful multidecade international investment in coronary artery disease (CAD) therapy. Improvements from “plain old balloon angioplasty” (“POBA”) to endovascular stenting and drug-eluting stents have shown impressive clinical and quality-of-life gains for patients with CAD. Based on large, randomized clinical trials in CAD, these technologies have resulted in universal reimbursement and wide penetration in clinical practice worldwide. Patients with acute myocardial infarction treated by endovascular techniques have fewer clinical events and improved survival. Individuals with CAD and angina, especially those with symptoms refractory to medical therapy, enjoy improved quality of life.

More than 9 million people in the United States and as many as 27 million in North America and Europe have atherosclerotic peripheral artery disease (PAD). Of these, ≈10% have classic claudication, another 40% experience atypical leg symptoms, and a smaller cohort suffer critical limb ischemia. Recent data have demonstrated that care offered for such individuals is now associated with large healthcare costs ($4.37 billion in 2001 among Medicare beneficiaries). These costs are comparable to or greater than those for other common cardiovascular diseases (eg, cardiac dysrhythmias, congestive heart failure, and cerebrovascular disease). In distinct contrast to the health gains for individuals with CAD, comparable advances have not been achieved for patients with PAD. Despite comparable PAD prevalence in 2008, patients with PAD continue to have higher mortality and worse quality of life than individuals with CAD. The well-structured international clinical research enterprise developed for CAD has not yet delivered endovascular therapeutic advances for most symptomatic patients with lower-extremity PAD. It is unclear whether this slow progress is due to differences in the vascular biology of PAD versus CAD, the smaller investment in lower-extremity clinical research by government agencies and device manufacturers, or trial design flaws and slow enrollment of patients into clinical trials by physicians treating patients with PAD.

The results of 2 recent clinical investigations highlight the importance of these issues and should provide a stimulus for large, well-designed, randomized clinical trials to evaluate current and novel endovascular PAD care approaches. These trials also outline the ongoing challenge faced by vascular clinicians who strive to deliver endovascular clinical care to millions of patients with symptomatic PAD. The 2 trials are remarkably similar in design, therapeutic implication, and limitations (Table).

In the current issue of Circulation, Werk et al report the results of the FemPac pilot trial, which randomized 87 patients with femoropopliteal PAD to percutaneous intervention with uncoated versus paclitaxel-coated balloon catheters. The primary end point of angiographic late lumen loss at 6 months was significantly reduced in patients treated with the paclitaxel-coated balloon, although this angiographic primary end point was obtained in only 69% of 45 patients treated with the paclitaxel-coated balloon at 6 months. Patients treated with the paclitaxel-coated balloon also had a significant reduction in target lesion revascularization at 6 months, which was maintained for 18 months. The previously published Thunder trial randomized 154 patients with stenosis or occlusion of a femoropopliteal artery to percutaneous intervention with uncoated balloons or paclitaxel-coated balloons (n=48), or uncoated balloons applied with paclitaxel in the contrast media (n=52). Similarly to FemPac, this small study demonstrated a significant reduction in the primary end point of late lumen loss and a significant reduction in target lesion revascularization at 6 months, which was maintained at 24 months. Thus, each trial demonstrated a signal of biological efficacy as arterial lumen size was preserved with use of a paclitaxel-coated balloon.

Unfortunately, both investigations were limited in design in a pattern that has become almost axiomatic of lower-extremity PAD endovascular clinical trials. Both FemPac and Thunder examined small sample sizes, enrolled heterogeneous patient populations, provided incomplete follow-up, and were designed to evaluate short-term angiographic primary end points that are not symptom based. In terms of enrollment criteria, clinical indications were quite variable (ie, including patients in Rutherford classes 0 to 5) and...
Table. Results of FemPac and Thunder Clinical Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sample Size</th>
<th>Angiographic Follow-Up Rates, n (%)</th>
<th>6-Month Late Lumen Loss</th>
<th>6-Month Angiographic Restenosis, n (%)</th>
<th>6-Month TLR</th>
<th>18- to 24-Month TLR</th>
<th>6-Month Deaths, n</th>
<th>6-Month Major Amputation, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>FemPac Rx (n=45)</td>
<td>31/45 (69)</td>
<td>0.5±1.1</td>
<td>6/31 (19)</td>
<td>9%</td>
<td>20%</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Control (n=42)</td>
<td>34/42 (81)</td>
<td>1.0±1.1</td>
<td>16/34 (47)</td>
<td>33%</td>
<td>48%</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Thunder Rx (n=48)</td>
<td>41/48 (85)</td>
<td>0.4±1.2</td>
<td>7/41 (17)</td>
<td>4%</td>
<td>15%</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Control (n=54)</td>
<td>48/54 (89)</td>
<td>1.7±1.8</td>
<td>21/48 (44)</td>
<td>37%</td>
<td>52%</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

TLR indicates target lesion revascularization; Rx, paclitaxel-coated balloon; and control, uncoated balloon.

Incremental success for lower-extremity PAD endovascular care is necessary. Interventional physicians of all specialties recognize that current endovascular therapies for the femoropopliteal segment are not yet ideal. In contrast to the coronary arterial bed, infrapopliteal arterial atherosclerosis frequently creates long, often calcified, and multisegmental stenoses; “runoff” (patent distal arteries) may be poor, leading to slow flow in the treated segment; and restenosis rates are moderately high even at short time points (eg, 1 year). The biological underpinnings of these adverse outcomes relate to the vascular biological heterogeneities that distinguish lower-extremity and coronary arteries.8 Thus, the ideal endovascular approach for a coronary artery may not be the ideal approach for the femoropopliteal segment, providing an opportunity for novel technology development based on vascular biological principles.

Preclinical data have demonstrated that use of paclitaxel-coated balloons in both coronary and peripheral arteries can create high local drug concentration and diminished neointimal proliferation, even when balloon-delivery exposure is brief. In both of these trials, balloons were coated with paclitaxel at a dose of 3 μg/mm², and a quantitative analysis of the paclitaxel balloon residue was performed after the intervention. In the FemPac study, an average of 2.8 mg per balloon or 3.7 mg per patient of paclitaxel was delivered with a dose range of 1.3 to 12.2 mg. The quantitative analysis demonstrated that >90% of the drug had been released. The results in the Thunder study were similar, with a mean dose of 4.7±3.5 mg administered per patient and with only 6.6% residue of the dose remaining on the balloon after the procedure. This method of drug administration was associated with improved 6-month angiographic restenosis rates of 17% versus 44% in the Thunder study and 19% versus 47% in FemPac. A major question remains as to whether the very unique physicochemical properties of paclitaxel (extreme hydrophobicity) make this 1 of very few agents that might function in this application, or if other agents could be similarly delivered with comparable efficacy.

Conclusions

What can we conclude from FemPac and related clinical trials of POBA-based paclitaxel delivery in femoropopliteal arterial disease? What is required if endovascular therapies using balloons alone are to achieve luster? First, both clinicians and patients must remember that the end point of interest for all lower-extremity endovascular trials should be efficacy in clinical PAD outcomes (eg, improvement of claudication symptoms and limb survival) and that this must occur in a relevant time frame (at least 1 year and ideally 5 years) with included de novo lesions, restenotic lesions after balloon angioplasty, and in-stent restenotic lesions (~35%). Lesions were relatively long (6.5 to 7.5 cm), and 15% to 27% of patients had total occlusions. Neither trial established complete blinding, which may directly affect rates of target lesion revascularization. Although each trial described the Rutherford clinical class at baseline (an approximate and nonobjective indicator of clinical PAD severity), the collection of this simple clinical symptom class was not available in almost 25% of subjects at 6 months or in 43% of subjects at 18 to 24 months. “Proof of principle” was claimed for paclitaxel delivery by balloon alone and, if true, constitutes a very exciting development in endovascular therapy. However, no pharmacological intervention would be considered safe or effective when used in <100 patients with incomplete 2-year follow-up.

More appropriate clinical end points are well defined for use in PAD clinical trials and serve as the only truly appropriate outcomes for which device implantation, approval for use, or reimbursement would be appropriate. These outcomes would include treadmill-measured pain-free or maximal walking distance, a 6-minute walk, or subjective measures of quality of life. Patients with PAD do not request and primary physicians do not refer individuals for PAD endovascular care in order to achieve improved late lumen loss or target lesion revascularization.

Despite these constraints, clinicians and vascular biologists alike will likely be impressed that both trials demonstrate significant reduction in the primary end point of late lumen loss (eg, 0.5±1.1 versus 1.0±1.1 mm and 0.4±1.2 versus 1.7±1.8 mm in FemPac and Thunder, respectively) and a significant reduction in the secondary end point of target region revascularization (eg, 9% versus 33% and 4% versus 37% in FemPac and Thunder, respectively). Likewise, there was a significant improvement in angiographic restenosis at 6 months in both trials. Could this approach of using a paclitaxel-coated balloon possibly work? Although a small trial (n=52) has demonstrated improvement in achievement of patency outcomes with paclitaxel-coated balloons used for in-stent restenosis in coronary arteries,6 the majority of interventional cardiologists remain extremely skeptical. Is this skepticism based on data or bias? As noted above, endovascular care initially demonstrated feasibility of POBA, followed by the clear superiority of bare metal stents over POBA, followed by an incremental clinical improvement with use of drug-eluting stents.7 Currently, most interventional cardiologists would lose sleep (figuratively and literally) over a shift back to POBA for coronary arteries because of the demonstrable risk of acute vessel closure.
minimal adverse events. Patients, clinicians, and payers in the
decade ahead will not accept late lumen loss or target lesion
revascularization as adequate surrogate end points. Second,
enthusiastic vascular specialists who treat lower-extremity
PAD by endovascular techniques alone could rapidly create a
“nonsustainable” health economic environment if such inter-
ventions are routinely deployed as the most costly and least
durable first-line therapy (eg, routine femoropopliteal stent-
ing for individuals with claudication symptoms). Clinical
benefit can already be achieved by POBA in many iliac artery
segments, as well as in short superficial femoral and popliteal
stenoses, with stenting reserved for longer lesions and those
with high rates of postdilation recoil or dissection.1 Third,
both investigators and clinicians should note that there are
beneficial evidence-based noninvasive therapies that reliably
improve claudication symptoms; these therapies remain un-
derutilized. Claudication pharmacotherapy (eg, cilostazol) or
supervised exercise should be more widely considered and
prescribed. Effective pharmacological or lifestyle interven-
tions are often constrained by health payers that effectively
incentivize invasive interventions. Finally, advancement of
the PAD endovascular evidence base will remain incomplete
until PAD clinical trials are designed with adequate sample
size, they recruit study populations rapidly, and they provide
robust benefit-risk clinical outcome data. This will require a
fundamental change in the vascular academic and clinical
care culture.

In most societies, balloons are used in times of celebration,
raising our hopes high in the air. Balloons can also effectively
treat stenotic coronary and lower-extremity arterial stenoses.
The recent paclitaxel endovascular lower-extremity PAD
trials may permit POBA to now also be construed as a method
of lower-extremity drug delivery that has demonstrated
“proof of biological activity.” The next steps in vascular
clinical research may potentially return the luster to the
balloon and improve the prospects of achieving improved
limb health for millions of individuals internationally.

Disclosures
None.

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