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EDITORIAL COMMENT

Ultrasound Plus Paclitaxel Trumps Drug-Coated Balloon*

Progress in the Periphery?

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In recent years, clinicians have witnessed an explosion in the number of novel technologies available to treat patients with symptomatic and limb-threatening peripheral artery disease (PAD). Traditional endovascular treatment for lower extremity femoral-popliteal PAD has consisted of angioplasty and bare-metal stents, but both drug-eluting stents (DES) and drug-coated balloons (DCB) have become increasingly utilized, owing to randomized data demonstrating better patency with these newer devices (1–3).

Despite the improvements that drug-elution technologies have afforded in the periphery, restenosis rates still remain suboptimal, particularly when compared to outcomes in the coronary tree (4), and adverse clinical events such as major amputation in the critical limb ischemia (CLI) population remain unacceptably too common (5). Moreover, the efficacy of DCB and DES for PAD is based predominantly on randomized trials that have compared these technologies to balloon angioplasty in simple, short lesion subsets. Whether similar benefits would be replicated in the more complex lesion subsets encountered in routine practice, and how specific drug-elution devices (e.g., DCB vs. DES) compare against each other remains largely unknown. In this regard, the current PAD climate is one in which novel treatment strategies have never been more available and attractive, but determining when and how to optimally apply these therapies to optimize individual patient outcomes has never been more challenging.

Paclitaxel is a lipophilic taxane that exerts antirestenotic effects by inhibiting microtubule breakdown and resultant smooth muscle cell and fibroblast proliferation (6). Paclitaxel has occupied a pivotal role in the PAD realm as randomized trials have demonstrated reductions in restenosis and target vessel revascularization in the femoropopliteal segment with balloon and stent platforms coated with this antiproliferative agent (1,3,7). One particularly important study, the THUNDER (Local Taxane with Short Exposure for Reduction of Restenosis in Distal Arteries) trial, demonstrated reductions in 6-month late lumen loss when paclitaxel was administered in DCB form compared to standard angioplasty. However, this same trial demonstrated that there was no benefit when standard angioplasty was followed by exposure to a paclitaxel-iodinated contrast solution delivered via catheter injection, thus implying that delivery mode is an important driver of drug efficacy (7). Indeed, alternative mechanisms of paclitaxel delivery using occlusion balloon devices and porous balloons have been successfully reported in the literature (8,9), but a comprehensive understanding of how to optimally deliver the antiproliferative drug in terms of vehicle and dose remains incomplete.

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In this issue of *JACC: Cardiovascular Interventions*, Gandini and Del Guidice (10) report the results of the PACUS (Ultrasound to Enhance Paclitaxel Uptake in Critical Limb Ischemia) trial, a single-center trial randomizing 56 CLI patients with femoropopliteal disease to either DCB angioplasty using the In.Pact Admiral paclitaxel-coated balloon (Medtronic, Santa Rosa, California) or ultrasound-facilitated paclitaxel delivery (US-PTX) arm (10). In the US-PTX arm, standard balloon angioplasty was performed in usual fashion at 1:1 sizing, then the lesion was treated with 60 s of local, intravascular ultrasound energy using the

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Genesis system (Cardioprolific Inc., Hayward, California). Following ultrasound treatment, a balloon was inflated distal to the lesion to create flow cessation, and a paclitaxel-iodinated contrast mixture was injected into the stagnant blood column and allowed to absorb into the vessel wall for 60 s. Mean lesion lengths were 169 and 164 mm, and occlusions were present in 71% and 54% of the US-PTX and control groups, respectively. Primary patency was better in the US-PTX group at 6 months, and rates of target lesion revascularization and amputation were significantly reduced at 12 months as well.

The authors of the PACUS trial are to be commended on many fronts. Thought leaders and stakeholders immersed in PAD care have repeatedly stressed the importance of having randomized trials that compare novel therapies to meaningful control arms (11). In this sense, regardless of results, the PACUS trial is a success by simply comparing a new treatment (ultrasound-facilitated paclitaxel delivery) to DCB, a therapy that some would consider to be current best practice for femoropopliteal disease. The lack of an angioplasty control arm and the inclusion of relatively long femoropopliteal lesions are welcomed departures from most prior randomized investigations.

That the PACUS trial included only patients with CLI is also noteworthy, as most trials of drug-elution devices for femoropopliteal disease have included only a small percentage of patients with rest pain or tissue loss (2,3,7). This is vital, as the demonstrable efficacy of novel PAD therapies may be less robust, or entirely different, in a CLI population where cardiovascular risk is higher, lesion phenotype is more complex, and infrapopliteal disease is much more common.

The PACUS trial results are also encouraging by virtue of suggesting that alternative drug delivery mechanisms may prove superior to existing DES and DCB platforms. Not only did ultrasound-facilitated paclitaxel delivery improve patency compared to DCB, it also reduced major amputation, which is arguably the most important limb-related endpoint for patients with CLI. As most interventionalists have migrated to a drug elution–first strategy first when treating femoropopliteal disease, this study suggests that existing DES and DCB strategies may not represent a panacea for patients with infrainguinal PAD. In this regard, the PACUS trial may fuel future efforts to discover innovative methods to combat vascular restenosis without necessarily relying on balloon and stent vehicles.

There are some important limitations of the PACUS trial. First, the experimental arm employed ultrasound and a different mode of paclitaxel delivery to outperform the DCB group. From a mechanistic standpoint, it is unclear if the mode of paclitaxel delivery, ultrasound application, or both acted synergistically to improve results. As the authors note, ultrasound treatment induces vasodilation and may increase drug uptake (12,13), but a clear understanding of the causal relationship among ultrasound, paclitaxel, and improved patency in this study will need further investigation. Also, more than one-half of patients deemed eligible for the study were excluded due to subintimal lesion crossing or need for stenting due to suboptimal angioplasty results. This implies that the ultrasound technology may not be generalizable to a significant proportion of femoropopliteal lesions. Finally, the sample size is small, and additional studies will be needed to replicate these findings, define optimal dosing and ultrasound treatment times, and determine whether this method outperforms other DCB brands and drug-elution devices. The lack of core laboratory analysis and the sparse details provided on concurrent below-knee interventions are limitations that should also be potentially addressed in the future.

The publication of the PACUS trial suggests that interventional PAD research is progressing in an enthusiastic and invigorating direction. Novel therapies are being compared to best available treatments, and meaningful endpoints relevant to patients and important stakeholders are finally being examined. Much remains to be learned in terms of how to tailor interventional device therapy to individual patients and lesions, and this clinical decision making will only become more complicated as health care value considerations become integrated into the process. From a clinician standpoint, this progress should engender an unheralded period of humility, curiosity, and intellectual reward. For patients and families affected by PAD, improved outcomes seem imminent.

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