

# Infrapopliteal Interventional Tools

To intervene in CLI means to change.

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It is with great pleasure that we review the “toolbox” for infrapopliteal interventional treatments primarily for critical limb ischemia (CLI), a clinical entity rapidly being recognized because of its increasing incidence and overall huge clinical and economic impact. An analysis of the most recent US and European data on the number of major and minor amputations performed yearly determined 160,000 to 180,000 per year in the US, with an estimated 10% yearly increase, and 40,000 to 50,000 yearly in Europe, for a combined estimate of >220,000 to 240,000 amputations yearly.<sup>1-4</sup>

Within 1 year of being diagnosed with CLI, 40% to 50% of the now 20 million diabetics in the US will experience a major amputation, and 20% to 25% will die.<sup>5,6</sup> Moreover, 30% to 50% of all amputees will face contralateral CLI and undergo a second limb (contralateral) amputation within 3 to 5 years of ipsilateral amputation.<sup>3,5,7</sup> It has been estimated that the total cost of treating CLI in the US alone is \$10 billion to \$20 billion per year; just a 25% reduction in amputations could save the US health care system \$2.9 billion to \$3 billion annually.<sup>3,4,8</sup>

It would do us all good to remember that an interven-

tion literally means “to intervene” or “to change,” and recent device technology advancements are resulting in a rapid change in the management of CLI. Perhaps our most important intervention or change should be one of basic education by enhancing the awareness of these new CLI tools. Increasing awareness alone could potentially increase the number of patients referred for infrapopliteal revascularization as compared to primary amputations. Primary amputations unfortunately still occur worldwide at an alarming rate. In a recent analysis of 417 CLI patients in the US, 67% had a primary amputation as their initial CLI treatment and less than half (49%) had any diagnostic vascular evaluation, with only 34% undergoing an ankle-brachial index (ABI) examination and 16% undergoing angiography.<sup>9</sup> It is my opinion, in 2006, that with the recent improvements in noninvasive vascular imaging, including MR angiography, multichannel CTA, and the safety of traditional angiography, that no CLI patient be scheduled for amputation without at least noninvasive vascular imaging, and that preferably they undergo limb salvage (LS) angiography before being scheduled for an amputation. Our health care industry's next intervention should be to change this pathway to amputation to a pathway of revascularization, especially with the dramatic improvement in



Figure 1. The 308-mm, cool-tip laser (Spectranetics, Inc., Colorado Springs, CO) provides both athero- and thromboablation without distal embolization (A). A 0.9-mm laser over a .014-mm wire crosses an occluded percutaneous transluminal angioplasty (PTA) into a pedal vessel (B). Excellent PTA flow after laser revascularization (C).

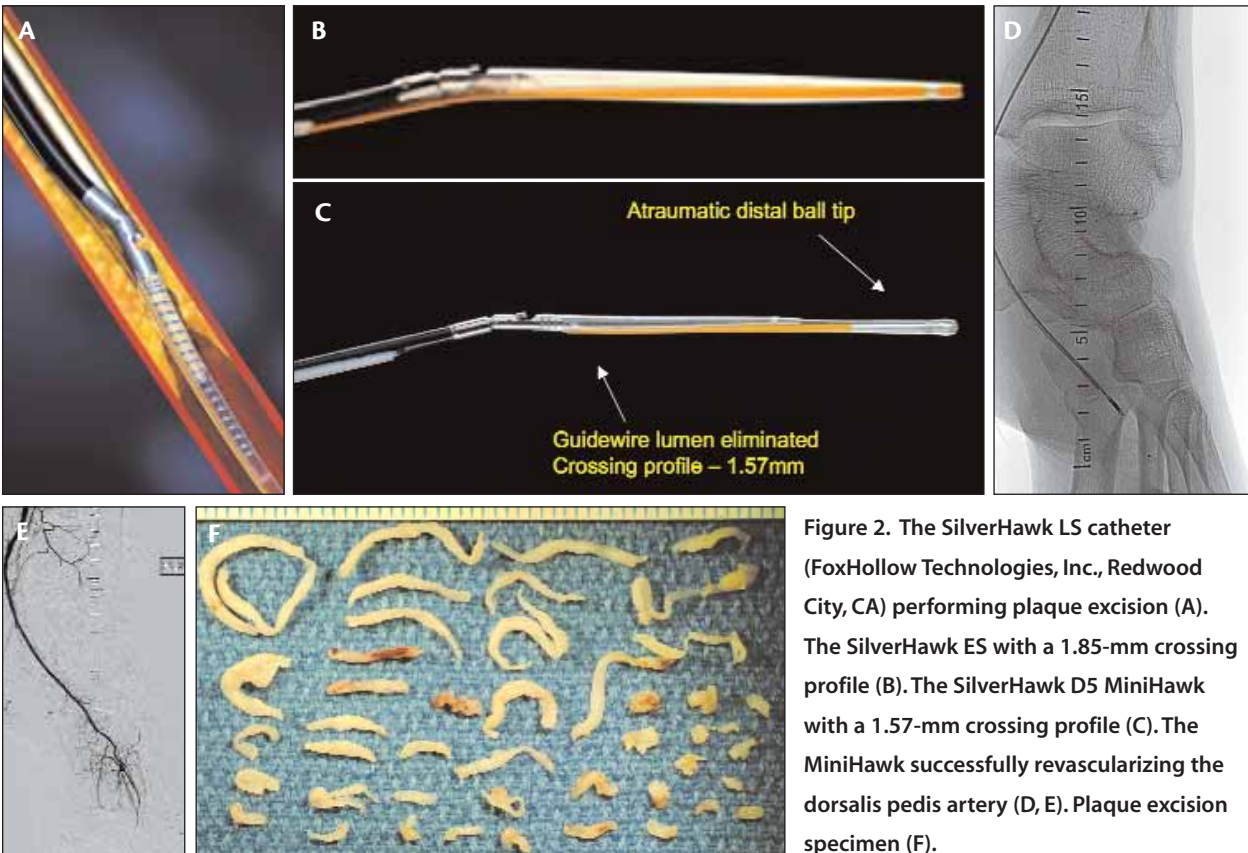


Figure 2. The SilverHawk LS catheter (FoxHollow Technologies, Inc., Redwood City, CA) performing plaque excision (A). The SilverHawk ES with a 1.85-mm crossing profile (B). The SilverHawk D5 MiniHawk with a 1.57-mm crossing profile (C). The MiniHawk successfully revascularizing the dorsalis pedis artery (D, E). Plaque excision specimen (F).

infrapopliteal diagnostic and treatment options that has occurred during over the last 3 years.

## BALLOON-BASED INTERVENTIONS

### Plain Old Balloon Angioplasty

Several excellent clinical tibial PTA results have been reported in the management of CLI. Dorros et al reported tibial PTA as a primary treatment in 235 CLI patients, with a 91% 5-year LS rate with low complications.<sup>10</sup> Faglia et al reported PTA as the first treatment in 993 diabetics with CLI. During  $26 \pm 15$  months of follow-up, 1.7% patients underwent major amputation, with 87 (8.8%) patients experiencing clinical restenosis. A 5-year primary clinical patency rate of 88% was reported.<sup>11</sup> In a meta-analysis of four PTA reports treating 702 CLI patients, the LS rates were 79% to 91%, with a low complication rate, and acceptable reintervention (9%-15%).<sup>12-15</sup> Kudo et al also recently reported a 10-year PTA experience in 111 CLI patients, with 0.9% periprocedural mortality and initial technical and clinical success of 96.4% and 92.8%, respectively.<sup>16</sup> The 5-year primary patency, assisted patency, and secondary patency were 31.4%, 75.5%, and 79.6%, respectively. The 5-year LS rate was 89.1%, concluding that PTA was safe and effective and potentially the primary treatment for CLI. The same authors recently published their 12-year experience of tibial PTA versus bypass surgery in 192 CLI patients, further defining tibial

PTA as safe and effective in treating CLI. Their conclusion was that tibial PTA is the initial treatment of choice in patients with CLI.<sup>17</sup>

Critical to the evolution of tibial interventions has been the development of smaller .018-inch and .014-inch wire exchange and delivery systems. The new-generation, dedicated tibial balloon designs have smaller profiles, thinner walls, longer shafts, higher strength, low pressure, hydrophilic coatings, tapering tips, and come in diameters as small as 1.5 mm and lengths of 12 cm. The Amphirion (ev3 Inc., Plymouth, MN) and Savvy Balloon (Cordis Corporation, a Johnson & Johnson company, Miami, FL) are but two of the examples of the new generation of dedicated tibial balloons. It was only 2 short years ago that I would do almost anything to avoid tibial PTA and its inevitable dissections, but today I have lowered my threshold for tibial PTA, utilizing the new-generation, dedicated tibial balloons, especially in those difficult-to-treat CLI patients with long diffuse disease. In addition, we now advocate longer (3-5 minute) low-pressure inflations and are increasingly happy with the results.

### Cutting Balloon

The cutting balloon (Boston Scientific Corporation, Natick, MA), originally designed for calcified coronary arteries, is now an option in tibial vessels, especially in more dis-

crete calcified lesions. The profile and tractability are somewhat inferior to the smaller PTA balloons, but Ansel et al reported a 1-year LS rate of 89.5% in 72 CLI patients with popliteal and infrapopliteal disease.<sup>18</sup> There were no perforations and only 20% required adjuvant stenting for residual disease or dissection, therefore defining its use in a difficult-to-treat CLI patient population. We have found particular use for the cutting balloon in heavily calcified discrete lesions in larger proximal infrapopliteal vessels.

The novel AngioSculpt Scoring Balloon (AngioScope Inc., Fremont, CA) was recently FDA approved for tibial disease and is a variation of the cutting balloon with a spiral, three-wire nitinol cage surrounding a semicompliant balloon. Scheinert et al reported a European multimember registry of 56 lesions in 43 CLI patients. Initial results included 98.2% successful deployment, 89.3% sole therapy, and 10.7% dissection rate.<sup>19</sup> Clinical results are pending but it is likely this therapy will be available in the US in the near future.

## PLAQUE (DEBULKING) INTERVENTIONS

### Excimer Laser Atherectomy

The pioneering laser work of Giancarlo Biamino has led to an understanding of the unique thrombus and atheroablative properties of pulsed excimer laser atherectomy. The 308-mm, cool excimer laser catheter delivers intense, controllable, ultraviolet energy in extremely short, pulsed durations, ablating tissue only on contact with reduced thermal injury and reduced potential for distal embolic complications (Figure 1A). The catheter diameter sizes range from 0.9 mm to 2.5 mm, making this technology especially applicable to infrapopliteal vessels and even pedal vessels in the foot. A 0.7-mm catheter will soon be available. The recent Turbo laser design has added 20% to 30% more optical fibers and energy with a "continuous on" mode, enhancing

the efficiency and ease of use. A novel sheath system is under investigation in the multicenter CELLO trial in which a 2-mm laser catheter is used in a four-quadrant technique to significantly increase the diameter of the lasered channel.

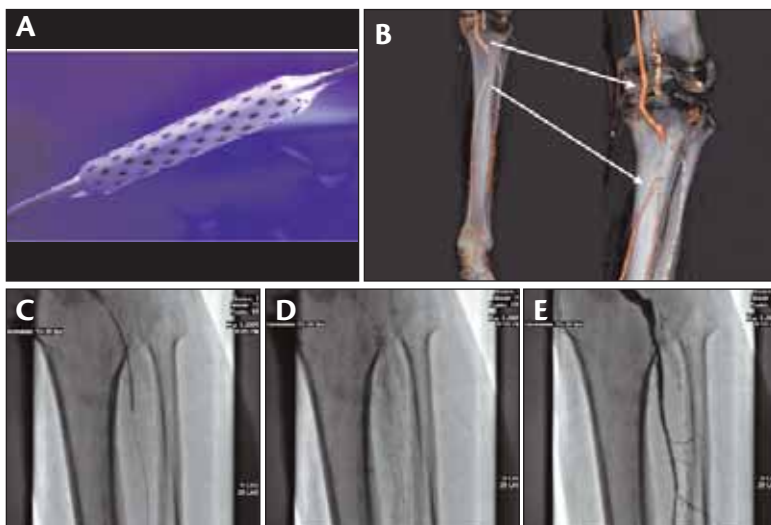
The recently reported landmark LACI trial enrolled 155 CLI patients with 423 lesions in 15 US and German sites.<sup>20</sup> All patients were considered poor or nonsurgical candidates with high comorbidities (Rutherford classes 4 [29%] and 5-6 [71%]). The 6-month LACI results included a 93% LS rate, with overall low periprocedural complications and a 6-month reintervention rate of 16%, with only 2% requiring bypass surgery. The LACI trial clearly demonstrated that endovascular interventions in CLI could achieve high LS rates (93%) in fragile and complex CLI patients with low complications who had no other surgical option. Similar results have been recently reported in the Belgium LACI and the CIS LACI-Equivalent studies (Figure 1B,C).<sup>21,22</sup>

### Plaque Excision

The SilverHawk plaque excision catheter allows plaque excision and retrieval without barotrauma. The SilverHawk is a monorail catheter with a carbide cutting blade system (8,000 rpm) that excises atherosclerotic plaque, which is collected in the nose cone for removal and potential tissue analysis (Figure 2A). The recently introduced SilverHawk DS, or "MiniHawk," is a lower-profile design allowing treatment in smaller infrapopliteal and pedal vessels (as small as 1.5 mm in diameter). The MiniHawk has a lower crossing profile (1.57 mm), two guidewire lumens, and the ability to perform plaque excision "off the wire" by retracting the guidewire out of the distal lumen, allowing further distal plaque excision into smaller pedal vessels. The ribbing of the nose cone has been removed allowing for the lower profile and increasing the

flexibility without decreasing the plaque-collecting capacity of the nose cone (Figure 2B-E). FoxHollow Technologies, Inc. and Merck & Co., Inc. (Whitehouse Station, NJ) are supporting several intriguing multicenter tissue analysis trials in an effort to analyze the extracted atherosclerotic plaque, attempting to unlock important cellular and genotypic information that has the potential for far-reaching global cardiovascular clinical implications (Figure 2F).

Kandzari et al recently reported a multicenter experience utilizing plaque excision in CLI patients with the first-generation SilverHawk device.<sup>23</sup> Excellent LS rates were reported, with a procedural success rate of 99% and an adverse event rate of 1%. There were no unplanned amputations. The emergence of the low-profile MiniHawk



**Figure 3.** The PolarCath balloon (Boston Scientific Corporation) (A). CTA of a CLI patient with a failing bypass (B). A PolarCath inflated after laser crossing of the graft-popliteal CTO (C, D). Excellent results after PolarCath use (E).

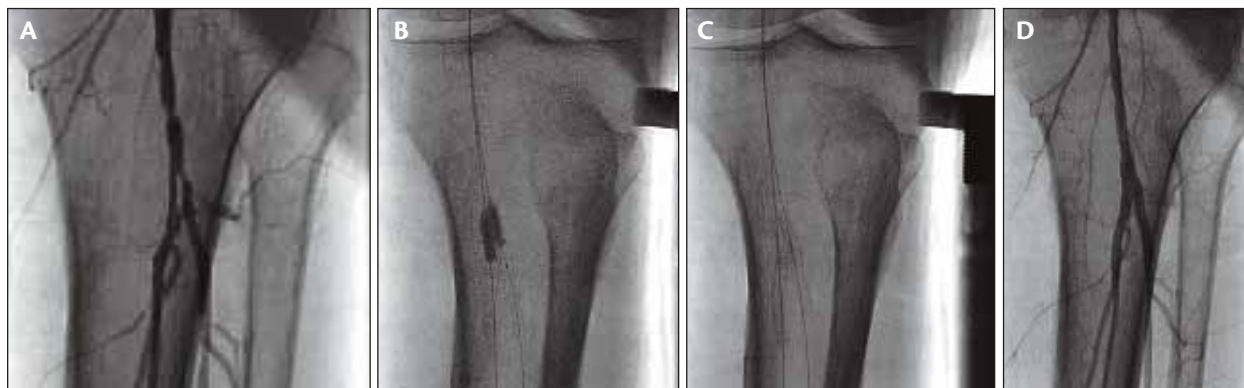


Figure 4. A CLI patient with suboptimal results after infrapopliteal laser/PTA (A). Kissing drug-eluting stents (DESs) positioned at the PTA-peroneal bifurcation (B, C). Excellent final results after infrapopliteal stenting (D).

will likely further extend the application of plaque excision into pedal vessels of the foot (Figure 2E).

## CRYOTHERAPY-BASED INTERVENTION

### Cryoplasty

The PolarCath is a novel PTA system that simultaneously dilates and rapidly cools the immediate tissue from 37°C to -10°C within contact to a known depth of only 510  $\mu\text{m}$ , therefore avoiding deep wall injury with less dissection.<sup>24</sup> The freezing occurs by the controlled inflation of a dual-balloon system with nitrous oxide instead of saline/contrast. In concept, this triggers a controlled form of dilation and smooth muscle cell death (apoptosis) that results in less elastic recoil and negative (constrictive) remodeling and less inflammatory response and, therefore, less cell proliferation (less neointimal hyperplasia). Cryoplasty has the potential for fewer dissections and less need for stenting in this more controlled plaque microfracture environment (8 atm pressure, 20-second balloon inflation time, and -10°C temperature) (Figure 3A).

The PolarCath is available in infrapopliteal diameter sizes down to 2.5 mm in diameter, with newer balloon lengths up to 8 cm, therefore enhancing its utility in treating CLI (Figure 3B-E). The interim results of the 16-site, multicenter, below-the-knee CHILL study (111 patients with infrapopliteal vessels treated between 2.5 mm and 5 mm) were recently reported.<sup>25</sup> The acute procedural success was 97%, with only eight cases of dissections (one was clinically relevant) reported. At a mean follow-up of 112 days, the freedom from major revascularization was 94%, with a 14% target limb revascularization rate. The 12-month data will soon be reported. We have just completed 1-year follow-up on 50 CLI patients utilizing the PolarCath in infrapopliteal lesions. Final analysis is underway, with a 1-year LS rate of 95%. There were very few dissections, and cryoplasty was found to be particularly beneficial in CLI patients with suboptimal results after infrapopliteal debulking.

## INFRAPOPLITEAL STENTING

### Bare Metal Stents

The absence of a reliable infrapopliteal stent has been a contributing factor to many interventionists not aggressively treating infrapopliteal disease. Even if only as a bailout as in PCI, infrapopliteal stents are a necessary component of the CLI tool box and now should be evaluated as a potential primary therapy. Fierling et al reported encouraging acute and 1-year results utilizing bare metal stents (BMSs) in infrapopliteal lesions.<sup>26</sup> Siablis et al compared BMSs versus DESs (Cypher, Cordis Corporation) as a bailout in CLI patients after PTA.<sup>27</sup> The 6-month LS rates were equal, but the DES group had less rest pain (7.7% vs 18.5%) versus the BMS group. The 6-month primary patency was reported as 68.1% for BMSs versus 92% for DESs.<sup>27</sup> Rand et al reported a randomized, prospective pilot study comparing PTA to the Carbostent (Sorin Biomedical, Modena, Italy), a balloon-expandable, coated infrapopliteal stent.<sup>28,29</sup> The 6-month angiographic patency with traditional or CTA was 83.7% for the Carbostent versus 61.1% for PTA. The LS rates were reported as equivalent, and a multicenter trial is underway.

Small-diameter (4 mm), self-expanding stents are now available with the introduction of the Xpert stent (Abbott Vascular Devices, Abbott Park, IL). The main attraction for this stent would be in patients with longer flow-limiting dissections, which may be propagated by balloon-expandable stenting and in lesions extending proximal into the popliteal artery. A randomized controlled trial is being launched, with James Joye, DO, as primary investigator.

### Drug-Eluting Stents

The initial excellent DES results in PCI versus BMS now mandate strong consideration for DES use in infrapopliteal disease (Figure 4A-D). Recent concerns regarding DESs in PCI likely will temper some enthusiasm for their use in the infrapopliteal arteries, but I would use caution drawing strong conclusions from PCI data because it is likely the

restenosis mechanism in treating PAD is different than in PCI, and the early DES results in treating CLI look promising. Scheinert et al randomized patients to Cypher versus PTA and reported a 12-month DES patency of 84% versus 53% for PTA.<sup>30</sup> Scheinert et al further randomized Cypher versus BMSs in 60 CLI patients; at 6.5-month mean follow-up, most variables analyzed significantly favored the Cypher DES. Angiographic follow-up at 6.5 months (mean) revealed that the in-stent obstruction rate of BMS was 17.4% versus 0% for DESs, and the in-stent restenosis rate of BMSs was 39.1% versus 0% for DESs ( $P=.0007$ ). Clinically, the BMS group exhibited a 10% amputation rate and a 23% target lesion revascularization rate, whereas the DES group had a 0% in-stent restenosis and amputation rate. Similar clinical results have been confirmed by Siablis et al in the bailout trial in which the target lesion revascularization, in-stent restenosis, and amputation rates were significantly reduced by utilizing a DES.<sup>27</sup> Stent fractures and deformations have not been reported thus far in infrapopliteal arteries by either Scheinert or Siablis during angiographic follow-up, potentially removing this clinical concern that has arisen in the femoropopliteal arteries.<sup>31-34</sup>

### DISTAL EMBOLIC INTERVENTIONS

The emergence of distal protection devices (DPDs) has raised concerns about the incidence of distal embolization (DE).<sup>35,36</sup> Distal macro- and microembolization can be particularly catastrophic in the CLI patient with poor and oftentimes only single-vessel runoff. Because no DPD exists that can be parked in an infrapopliteal vessel, and CLI patients are particularly susceptible to DE, we have advocated upstream protection by optimizing our anticoagulation and antiplatelet strategies by using bivalirudin and GP IIb/IIIa inhibition during all infrapopliteal interventions. The combination has been shown to have benefits in PCI patients with diabetes, small complex vessel anatomy, visible thrombus, and acute symptoms that correspond to our CLI patient population.<sup>37,38</sup> The safety and feasibility of direct thrombin and GP IIb/IIIa inhibition during CLI peripheral interventions has been reported, but validating randomized multicenter data are pending.<sup>39,40</sup> I believe this upstream

protection provides benefits with distal microembolization and platelet aggregation, which likely occur in all of our CLI patients with inherent compromised distal microcirculation.

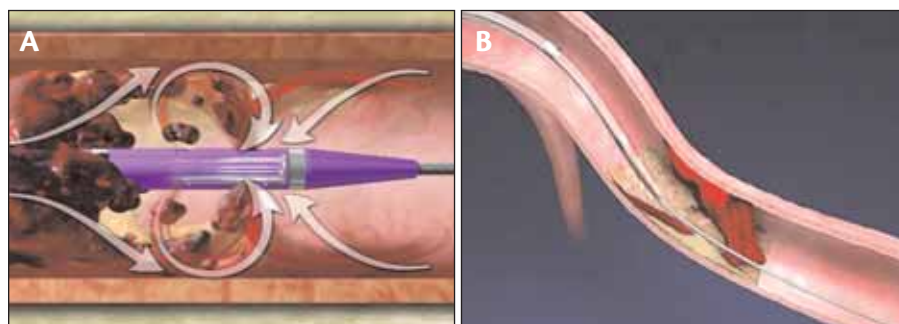
Once distal atheroembolization or thromboembolization occurs, mechanical thrombectomy tools are available but are limited by the small vessel sizes. The AngioJet (Possis Medical, Inc., Minneapolis, MN) is particularly effective in removing periprocedural thrombus, but it is somewhat less effective versus atherosclerotic debris; we have used it successfully in vessels down to 2.5 mm in diameter (Figure 5A). Similarly, the 6-F Pronto V3 Extraction (Vascular Solutions, Inc., Minneapolis, MN) can be used and may be more effective in removing small particulate debris. The novel Rinspiration Catheter System (FoxHollow Technologies) provides concurrent spray-action rinse and aspiration to facilitate removal of both thrombus and particulate embolic debris also in vessels down to 2.5 mm in diameter using the 6-F coronary Rinspirator (Figure 5B). The larger 7-F peripheral Rinspirator can also be used in the femoropopliteal vessels both before and after intervention, with a strategy to clear the vessel of debris before intervention, therefore facilitating the definitive intervention and decreasing distal macro- and microembolization.

### OTHER FUTURE TOOLS

Infrapopliteal absorbable metal stents (AMSs) (Biotronik GmbH & Co., Berlin, Germany) have been reported in a recent series of pilot studies.<sup>41-44</sup> Twenty CLI patients were treated and, with follow-up of 24 Kaplan-Meier analyses, an LS rate of 94.7% and a primary patency rate of 73.3% were reported. The prospective, randomized, multicenter AMS Insight I trial is currently set to enroll in Europe, and enrollment in an equivalent US study (Insight II) is planned in 2007. Importantly, the AMS was found to have no systemic effects by serologic testing and to be totally absorbed by IVUS, and is compatible with MRA/CTA. A combination of drug-eluting technology with AMS appears particularly appealing and is under investigation.

The Orbital Atherectomy System (OAS) (Cardiovascular System, Inc., St. Paul, MN) is a novel investigational diamond-coated rotational atherectomy device capable of

achieving a maximum of 200,000 rpm, with crowns from 1.2 mm to 2 mm in diameter. Animal studies have shown that 94% to 99% of particles were  $<0.5 \mu\text{m}$  in diameter and were therefore capable<sup>45</sup> of removal through the normal reticuloendothelial system. A US pivotal trial in 124 patients is underway, with no data yet reported. The theoretical advantage of OAS



**Figure 5.** The AngioJet fracturing and removing thrombus using the Venturi effect (A). The Rinspiration spray-action rinse and aspiration mode of action (B).

would be in the highly calcified and recalcitrant lesions that continue to pose a challenge to our existing CLI tools.

## CONCLUSION

Our CLI toolbox is not as bare as it once was. More than a dozen novel interventional technologies have exploded onto the scene in just the last 3 years. The biggest challenge to the health care system now is to provide an educational and awareness intervention, with the immediate goal to enhance the awareness that these tools exist. The long-term goal should be to decrease the number of primary amputations still performed today still without the consideration of revascularization as an intervention. To intervene and change this referral pattern is just as important a tool, if not more important, than all of our novel infrapopliteal device technologies. ■

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