

# TVR Reduction in the SFA

How do current TVR reduction rates compare with earlier values?

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Although endovascular techniques have markedly improved over the past decades, the important rates of restenosis and the frequent need for target vessel revascularization (TVR) remain challenging when nominating any endovascular approach as the gold standard technique. Particularly in areas as difficult as the femoropopliteal tract, long-term procedural success is hindered by extensive plaque burden, as well as numerous external mechanical stressors. Long (TASC II C and D), severely calcified (grade 3–4, > 270° calcium) lesions in the distal femoropopliteal segment in patients with critical limb ischemia with multilevel disease and significant runoff still have high TVR rates.

## PLAIN OLD BALLOON ANGIOPLASTY

Initial results with plain old balloon angioplasty (POBA) were extremely disappointing, as patency rates between 25% and 40% are reported after 1 year.<sup>1</sup> Balloon injuries (shear stress formation during inflation), negative arterial remodeling, excessive neointimal proliferation, elastic recoil, flow-limiting dissection, and lack of scaffolding are responsible for these undesirable results. High levels of bailout stenting, varying between 10% and 40%, were noticed in different randomized trials.

## MODERN GENERATION OF NITINOL STENTS

To solve the problem of lack of scaffolding, first balloon-expandable stents and thereafter self-expanding elgiloy stents were introduced. Because of balloon-expandable stent crush problems in a vessel where external compression forces of more than 1 kg are present, and a rigidity issue with elgiloy stents, the TVR rates were catastrophically high—in the range of 60% to 80% after 1 year.<sup>2</sup>

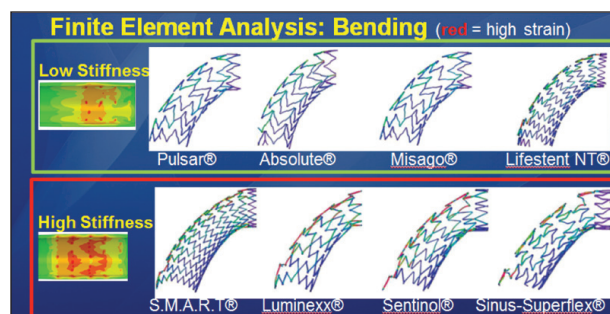
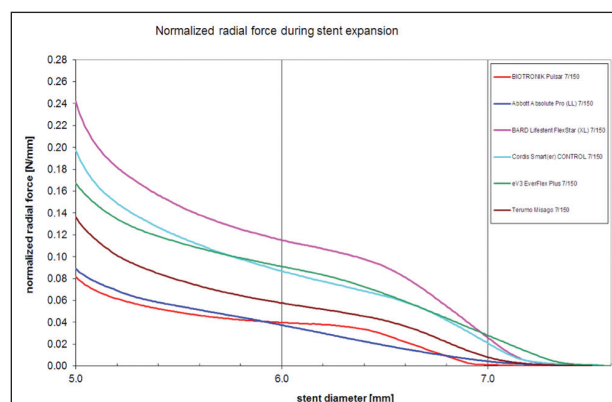


Figure 1. Advanced numerical models (ie, finite element models) offer interesting insights in the mechanical behavior of stents during bending and torsion tests.

After years of stagnation, self-expandable nitinol stents were introduced in the peripheral vascular area. Although very promising in the beginning because of their improved radial strength, flexibility, noncrushing properties, and high scaffolding potential, the FESTO database showed the problem of metallic fractures (directly linked to in-stent restenosis), particularly in longer lesions.<sup>3</sup> The first generation of self-expanding nitinol femoral stents were especially susceptible to this complication and showed fracture rates between 13% and 52% (longer lesions > 16 cm).

Recent larger trials have shown that the introduction of modern-generation nitinol stents significantly improves vessel patency and TVR rates for short- to moderate-length lesions (up to 15 cm). Longer stent lengths, greater flexibility, moderate chronic outward force (COF), sufficient radial resistive force, and high crush resistance are the key properties for successful superficial femoral artery (SFA) stenting with this new generation of stents.

Longer stent lengths prevent stiff overlapping areas that are prone to in-stent restenosis. To this point,



**Figure 2.** The modern-generation nitinol stents offer a low COF with homogenous spread along the full lesion length (flat expansion force curve), which also creates less concern for precise vessel sizing.

stent fracture rates in the SIROCCO 2 arm were much lower than in the SIROCCO 1 arm, just because of lower stent overlapping percentages.<sup>4</sup>

Advanced numerical models (Figure 1) now offer interesting insights into the mechanical behavior of stents during bending and torsion tests. Modern, completely changed stent designs allow reduced levels of stress during these bending/torsion maneuvers, which increases the safety and efficacy of the procedure and reduces TVR rates in the medium term.

Stent design also influences COF, the radial force at expansion of a stent to achieve the preset diameter. The COF is also influenced by strut thickness, strut width, and the number of connectors. Several animal trials showed an exponential increase in stresses on the vessel wall (intramural stress) if the COF is too high (ie, significant oversizing), resulting in a profound long-term histological response including exuberant neointimal hyperplasia and early restenosis.<sup>5</sup> Modern-generation nitinol stents offer a low COF, homogenous spread along the full lesion length (flat expansion force curve, Figure 2), which also creates less concern for precise vessel sizing.

Once the stent is implanted, a restenotic response starts, and a new tissue mass begins to develop. Adequate radial resistive force (applied all around the circumference of the stent) and crush resistance (applied at one area of the stent) are essential to deal with this growing tissue mass and to prevent stent collapse.

A unique design that responds to all of these properties is the vascular mimetic implant (Supera, Abbott Vascular). Although vessel preparation and device deployment are more difficult and cumbersome,

Supera offers outstanding performance in “coral reef” calcified femoral and popliteal arteries, which is confirmed by very good patency rates (around 85%) and 0% fracture rates.<sup>6</sup>

Based on these newer insights in stent technology and behavior, patency rates between 72% and 85% after 1 year can be achieved for lesions up to 15 cm. Even in the long run, we still notice patency rates of 77% and 71 % (at 3- and 5-year follow-up).<sup>7</sup> Unfortunately, for longer lesions, patency rates drop to 64%.<sup>8</sup>

## DRUG-COATED BALLOONS

As safe and efficient as the latest generation of nitinol stents is, it remains a metallic implant, potentially irritating the vessel and creating an inflammatory response. Based on this doubt, and especially for shorter lesions (TASC II A and B), the “leave nothing behind” strategy is gaining more and more enthusiasts. This enthusiasm is meanwhile confirmed by many well-controlled, randomized trials that show the superior efficacy and noninferior safety outcomes of drug-coated balloons (DCBs) compared to POBA in the same areas as the newer nitinol stents.<sup>9-13</sup>

A few recently presented major pivotal trials, IN.PACT SFA I and II (331 patients at 57 sites; In.Pact Admiral, Medtronic, Inc.)<sup>14</sup> and LEVANT 2 (476 patients; Lutonix, Bard Peripheral Vascular)<sup>15</sup> confirm the initial findings of favorable freedom from clinically driven TLR rates at 1 year (97.6% and 87.7%, respectively) in TASC II A and B lesions (89 and 63 mm, respectively).

More and more, DCB-based treatment is considered the new standard of care for treating TASC II A and B lesions, if they are not calcified and > 270° in circumference. The old style of performing angioplasty—well sized, step by step increasing the pressure sufficiently to deal with the lesion, prolonged gradual inflation for 2 to 3 minutes, and total deflation before retrieving the balloon—is key to success. On the other hand, geographical misses (initial percutaneous transluminal angioplasty outside the range of DCB inflation) will have a negative impact on the final TVR results and should be avoided.

Of course, not all DCBs are the same. Poor deliverability platforms and loss of the antiproliferative drug during handling, insertion, and delivery are, at this moment, major drawbacks to some of the devices. The coating and the loading technique are essential to deal with drug-coating integrity and maximal drug transfer efficiency to the vessel wall and not to the distal vascular bed.

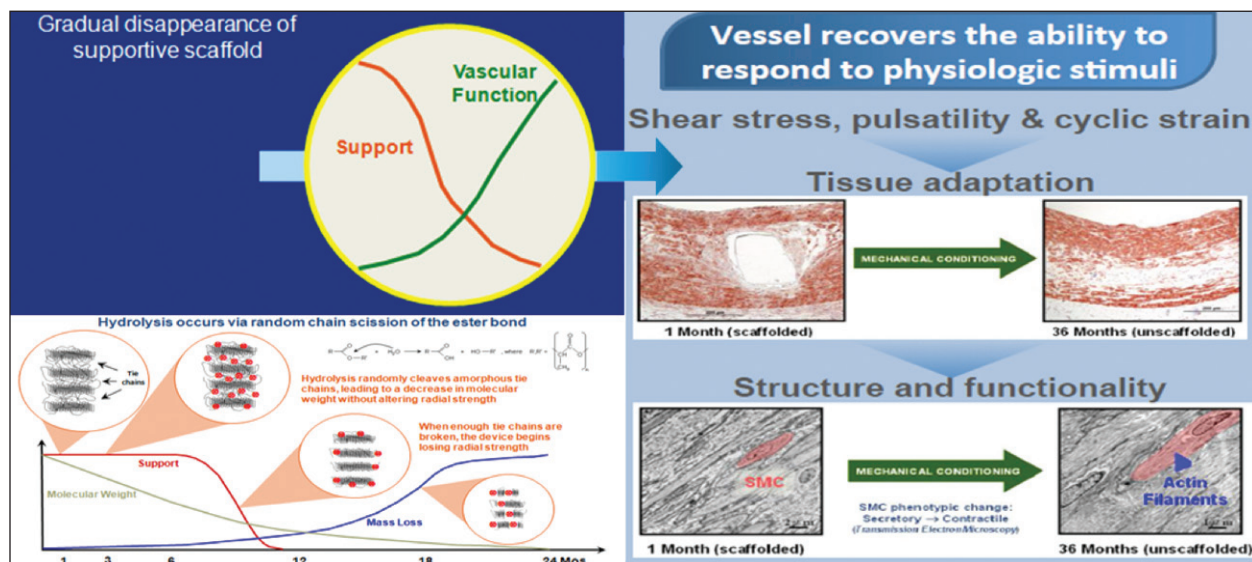


Figure 3. The everolimus-coated Esprit BVS working mechanism (Abbott Vascular).

In calcified lesions and longer lesions (TASC II C and D), there is a greater need for scaffolding after DCB use. Especially with flow-limiting dissections and residual stenosis > 30%, stent implantation, although focal (spot-stenting) if possible, is mandatory most of the time. Two single-center registries by Schmidt<sup>16</sup> and Zeller<sup>17</sup> show promising patency results of 77.6% and 76.1%, respectively, with bailout stent ratios of 24% and 19%. The recently presented 1-year outcomes of the first 655 IN.PACT Global Study patients treated with the IN.PACT Admiral DCB (Medtronic, Inc.) in a real-world SFA-pathology setting with greater complexity confirm the earlier trial findings, including a clinically driven target lesion revascularization (TLR) rate of 8.7%. A cost-effectiveness analysis in the same trial shows a clear economic benefit in the DCB group over the POBA group.<sup>18</sup>

This economic advantage may be significantly affected when there is a need to combine the treatment with debulking devices (with or without embolic protection devices), although the results of the DEFINITIVE AR study look promising. The combined use of TurboHawk (Covidien) with the Paccocath DCB (Medrad) showed significantly higher technical success rates (89.6% vs 64.2%) and lower dissection rates (2% vs 19%) compared to the DCB-alone group.<sup>19</sup> One-year results have more to clarify concerning this approach.

## DRUG-ELUTING STENTS

Another more expensive but already “longer-term” proven way to deal with lowering TVR rates and increasing the safety of SFA procedures is the use of

drug-eluting stents (DES). The combination of scaffolding the vessel wall and blocking smooth muscle cell proliferation seems to be an ideal technique in the long run, especially in challenging, long, and calcified vessels. The 4-year results of the ZILVER PTX randomized trial,<sup>20</sup> as well as the Single-Arm Study long lesion subanalysis<sup>21</sup> and the Japan PMS long lesion subanalysis, show clear benefits in terms of safety and efficacy with the Zilver PTX polymer-free paclitaxel-eluting stent (Cook Medical).

## COVERED STENTS

Covered stents can play an important role in reduction of TVR rates, especially when used in challenging cases. The prospective, multicenter VASTAR trial, which randomized 72 subjects in the heparin-bonded Viabahn (Gore & Associates) arm (vs 69 in the bare-metal stent group), showed a clear benefit of this device in longer lesions (mean lesion length, 19 cm in the Viabahn group). Patency rates of 78.1% and freedom from TLR rates of 84.6 % were, in an important, statistical way, much better than the bare-metal stent group results in this “long-lesion” trial.<sup>22</sup>

## BIORESORBABLE STENT TECHNOLOGY

To overcome the limitations of permanent implants (creating chronic physical irritation) while offering an initial supporting scaffold to overcome the problem of acute recoil, there has been a gradual introduction of resorbable scaffold technology for the SFA. These devices function as an effective scaffold without the permanence of a metallic implant, avoid the chronic

foreign body inflammation, and facilitate positive arterial remodeling by returning the vessel to its natural uncaged state with preserved vasoactive function. Trials with non-drug-eluting resorbable scaffolds, such as PERSEUS (with the PLLA-polymeric balloon-expandable Igaki Tamai device, Igaki Medical Planning Company), STANCE (with the self-expandable polymeric PLGA Stanza v 1.0 scaffold, 480 BioMedical), GAIA, and REMEDY (with the balloon-expandable PLLA Remedy scaffold, Igaki Medical Planning Company) were not able to show favorable outcomes compared to currently available devices. The initial lack of wall apposition combined with the unblocked inflammatory reaction during the resorption process itself are probably responsible for these disappointments.

Nevertheless, the introduction of drug-releasing properties and the creation of new designs can overcome these limitations. The 1-year results with the everolimus-coated Esprit bioresorbable vascular scaffold (BVS; Abbott Vascular) (Figure 3) are extremely promising (TLR rate of 8.8% and binary restenosis rate of 12.9%).<sup>23</sup> We also expect positive results from the SPRINT trial (with the paclitaxel-eluting Stanza DRS device, 480 BioMedical) in the coming months. Another approach to add an antiproliferative effect to bioresorbable treatment is to combine the bioresorbable scaffolds with DCB predilatation. Studies are currently being performed to evaluate this technique.

## CONCLUSION

Neointimal hyperplasia formation remains a challenging problem in the SFA. Nevertheless, engineers and device manufacturers have remarkably improved the clinical outcomes for our patients. The shorter TASC II A and B lesions have been tackled with the “leave nothing behind,” cost-effective DCBs and are accepted more and more as the standard of care. The more difficult TASC II C and D lesions require a drug release or creation of a mechanical barrier toward intimal hyperplasia with covered stents. The available drug-releasing therapies are DCB angioplasty with focal bailout stenting with newer generations of nitinol self-expanding stents that are available in longer lengths and are more bending-, torsion- and compression-resistant (and with the correct crush resistance and appropriate chronic outward and radial resistive forces) or the implantation of paclitaxel-eluting stents. The future looks even more bright if the combination of antiproliferative drug release and bioresorbable scaffolds can extend the initial promising results in a larger number of patients with longer follow-up. ■

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