

# The SAVAL Trial

Details on the design and rationale behind this randomized trial studying infrapopliteal drug-eluting stent use for critical limb ischemia.

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Prompt endovascular or surgical revascularization is recommended to restore distal perfusion, minimize tissue loss, and maintain quality of life for patients with critical limb ischemia (CLI).<sup>1</sup> The major advantage of endovascular treatment compared to surgical bypass is lower periprocedural morbidity and mortality, which is a concern in typical patients with CLI who are older, frail, and often present with systemic atherosclerosis, diabetes mellitus, and elevated risk for cardiovascular events. Patients with CLI presenting with infrapopliteal atherosclerotic lesions of the tibial or peroneal arteries are an especially challenging population because restoring vessel patency is considerably more difficult in infrapopliteal lesions compared to those in the femoropopliteal segment.

Despite the obvious advantages of an endovascular approach in patients with significant systemic comorbidities, percutaneous transluminal angioplasty (PTA) results remain suboptimal in infrapopliteal lesions.<sup>2</sup> Short coronary drug-eluting stents (DESs) have been evaluated in infrapopliteal lesions in several randomized controlled trials, demonstrating superior patency and freedom from reintervention with DES compared to PTA,<sup>3-5</sup> with a sustained clinical benefit through 5 years.<sup>6</sup> However, no DES is indicated in the United States for infrapopliteal use, and coronary stents are not well suited for the hostile infrapopliteal segment. A DES for dedicated infrapopliteal applications should be available in longer lengths to accommodate long tortuous lesions, provide adequate radial force to prevent stent collapse and restenosis, yet remain flexible enough to avoid fracture when subjected to torque and extravascular compressive forces.

The SAVAL trial was designed to provide level 1 evidence of the clinical utility of a DES that is specifically intended for infrapopliteal applications. Investigation of this DES was arranged through the FDA Breakthrough Devices Program (formerly the Expedited Access Pathway), which is intended to facilitate development and expedite the review of breakthrough technologies.<sup>7</sup>

## TRIAL DESIGN

A total of approximately 301 patients with CLI undergoing infrapopliteal endovascular treatment are planned to be enrolled in the SAVAL trial (NCT03551496), which includes two phases. The first phase is a global, prospective, multicenter, randomized investigation designed to evaluate the safety and effectiveness of an infrapopliteal DES (Saval™ DES BTK, Boston Scientific Corporation) in patients with CLI. Approximately 201 patients with CLI (Rutherford class 4 and 5) will be randomly assigned (2:1) to the DES or PTA arms at up to 50 centers in the United States, Europe, and Japan. The primary objective of the randomized study is to demonstrate superior effectiveness and acceptable safety of infrapopliteal DES treatment versus PTA in patients with CLI.

The second phase of the SAVAL trial is a nonrandomized, single-arm study of 100 patients treated with the Saval™ DES BTK. Enrollment for this phase will commence after enrollment is complete in the randomized phase, with identical participating centers, eligibility criteria, procedures, outcome measures, and follow-up assessments. The purpose of the nonrandomized phase of the trial is to collect additional safety and efficacy data on patients who undergo implantation of a Saval™ DES BTK.

## PATIENT ELIGIBILITY

Key eligibility criteria include Rutherford class 4 or 5 disease, life expectancy > 1 year, no previous surgery in the target vessel, no previous or planned major amputation in the target limb, and absence of significant systemic comorbidities such as renal failure, New York Heart Association class IV heart failure, or symptomatic coronary artery disease. Importantly, limb hemodynamics will be collected at study enrollment and at all follow-up visits but not used as an inclusion or exclusion criteria. Inclusion criteria assessed intraprocedurally include the presence of one target lesion per vessel in no more than two infrapopliteal arteries in a single limb, reference vessel

diameter of 2.5 to 3.75 mm, total lesion length  $\leq$  70 mm ( $\leq$  140 mm after approval for stent overlap), and lesion location at least 4 cm above the ankle joint.

## STUDY PROCEDURES AND FOLLOW-UP

Patients will be randomly allocated to undergo infrapopliteal treatment with the self-expanding, nitinol, paclitaxel-eluting Saval™ DES BTK or PTA. This DES is specifically designed to optimize flexibility, radial/compressive strength, and fatigue properties for durable performance in infrapopliteal arteries. Commercially available PTA balloons, selected at the investigator's discretion, will be used as the comparator.

Adjunctive therapies for treating the target lesion, such as drug-coated balloons, atherectomy, or radiation therapy, are not permitted in the study. Anticoagulation and antiplatelet therapy will be administered before and during the procedure, according to the standard medication regimen at each center. Dual antiplatelet therapy is required in all patients for 6 months and is strongly recommended for 1 year in patients treated with the DES.

Patients will return for clinical and imaging follow-up at 1 month, 3 months, 6 months, and annually for 3 years.

## OUTCOMES

The primary effectiveness endpoint of the randomized trial is primary patency at 6 months. Primary vessel patency will be evaluated by duplex ultrasound on a per-lesion basis. Primary patency is a binary endpoint determined by duplex ultrasound measurement of flow (vs no flow) in the absence of clinically driven target lesion revascularization (TLR) or bypass of the target lesion. The primary safety endpoint of this trial is freedom from major adverse limb events and postoperative death (MALE-POD) at 6 months. This is a composite outcome including MALE (above-ankle amputation of the index limb or major reintervention [eg, bypass or interposition graft, thrombectomy, thrombolysis]) and POD (death within 30 days of index procedure). The MALE outcome has been endorsed by the Society for Vascular Surgery and FDA, and it is a primary endpoint in the ongoing BEST-CLI trial.<sup>8-10</sup> The single-arm study has a 12-month primary safety endpoint based on MALE-POD criteria, and efficacy information will also be collected.

Additional outcomes to be assessed include unplanned readmissions through 30 days, as well as hemodynamic outcomes and health-related quality of life (EuroQoL five dimensions and Vascular Quality of Life Questionnaire) through 1 year. Patency, clinically driven TLR, wound assessment, major amputations, Rutherford classification, and adverse events will be evaluated through 3 years.

Wound characteristics will be documented at each follow-up visit in patients with minor tissue loss, ischemic ulcer, or focal gangrene (Rutherford class 5) and evaluated by an independent blinded reviewer.

## DISCUSSION

Revascularization remains the cornerstone of therapy for CLI and is recommended by the professional guidelines.<sup>11,12</sup> The ongoing BEST-CLI trial may provide further insight into selective treatment strategies for these challenging patients. Although the specific role of surgery versus endovascular therapy remains uncertain, an endovascular-first approach has been recently advocated.<sup>13</sup>

For patients undergoing endovascular intervention, there is currently no DES that is approved for infrapopliteal applications in the United States. The aim of the SAVAL trial is to determine if a DES specifically developed for the infrapopliteal segment offers superior patency and acceptable safety compared with the current standard of care (PTA). The regulatory application for this trial will receive priority review by the FDA given the novelty of the device and because of the need for more effective treatment options in this patient population.

It should be noted that after the SAVAL trial had begun enrollment, the meta-analysis by Katsanos et al voiced concern regarding increases in late mortality seen after the use of paclitaxel-coated balloons and paclitaxel-eluting stents in the femoral and popliteal arteries.<sup>14</sup> This issue has been closely followed by the FDA and Boston Scientific Corporation. After the release of the updated FDA letter to treating physicians in March 2019,<sup>15</sup> the SAVAL trial informed consent document is being modified to reflect the following: the acknowledgment of a potential increased rate of mortality associated with paclitaxel-coated devices used to treat peripheral artery disease, the impact that this mortality signal may have on benefit-risk considerations for patient participation in the trial, and the need for diligent review and follow-up of all trial participants by the Data and Safety Monitoring Board.

## CONCLUSION

Given that CLI is underdiagnosed, increasing in prevalence, and responsible for significant risk to life and limb, considerable efforts are needed to raise disease awareness, refine diagnostic algorithms, and establish evidence-based treatment pathways. The SAVAL randomized trial is a first-of-its-kind study that utilizes a DES that is specifically developed for infrapopliteal applications. ■

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