Late-breaking clinical trials, Vascular Annual Meeting, Denver, Colorado, June 11-14, 2009


Objective: Whether endovascular repair of abdominal aortic aneurysm (AAA) reduces midterm morbidity and mortality compared with traditional open repair remains unclear.

Methods: Eligible patients had AAA for which repair was planned and that had (1) a maximum diameter of at least 5.0 cm, or (2) a maximum diameter of at least 4.5 cm plus rapid enlargement or saccular morphology, or (3) an associated iliac aneurysm ≥3.0 cm. Patients had to have completed all preoperative evaluations, be a candidate for both procedures, and meet the manufacturer’s indications for the endovascular system that might be used. Patients were randomized to endovascular repair with any Food and Drug Administration-approved system or to open repair and monitored for up to 2 years. The primary outcome was all-cause mortality. Secondary outcomes included (1) procedure failure (failure to complete the repair, additional aortoiliac procedures, unplanned procedures ≤30 days, and secondary therapeutic procedures), (2) days in hospital and intensive care units, (3) major morbidity at 1 year, and (4) health-related quality of life. Aneurysm-related mortality was not a prespecified outcome but will be presented for comparison with other trials.

Results: Between October 2002 and April 2007, 881 patients were randomized at 42 Veterans Affairs medical centers. Randomized patients had a mean age of 70, 99% were men, and 43% had an AAA <5.5 cm. Vital status was available on all patients. Outcome data will be presented in 2 years.

Commentary LB1: At the time of oral presentation, the trial investigators reported that 95% of enrolled patients (99.3% male) received their assigned repair within a mean of 3 weeks after randomization.

Total mortality in this 2-year analysis did not differ between endovascular and open groups (7% vs 9.4%, \(P = .19\)). However, endovascular repair had an early survival advantage: 30-day mortality was significantly lower compared with open repair (0.2% vs 2.3%, \(P = .006\)), with both rates lower than previously reported by Comparison of Endovascular Aneurysm Repair with Open Repair in Patients with Abdominal Aortic Aneurysm (EVAR-1) and Dutch Randomised Endovascular Aneurysm Management (DREAM) investigators. Secondary procedures were more common after endovascular repair, but the investigators did not observe an increased late mortality after endovascular repair by the 2-year follow-up. There was no difference in quality of life indices. The study is scheduled to end in 2011 and the investigators caution that longer-term follow-up is necessary to more fully compare the two treatments.

LB2. Interim Report on the Zilver® PTX™ Clinical Study. Dake MD; for the Zilver® PTX™ Investigators.

Objectives: The Zilver® PTX™ Drug-Eluting Peripheral Stent (DES) is undergoing clinical study to evaluate its potential for improving the treatment of femoropopliteal artery disease. The clinical study includes 1000 patients treated with the DES. Approximately 240 DES patients were enrolled in the randomized arm of the study, and 760 DES patients were enrolled in the registry arm of the study. Enrollment is complete, and this is an interim report of registry outcomes, including 2-year follow-up results.

Methods: The Zilver® PTX™ Registry is a prospective, multicenter, single-arm study with relatively broad inclusion criteria (eg, no maximum lesion length, de novo or restenotic lesions, including in-stent restenosis). The end points include event-free survival (EFS) and freedom from target lesion revascularization (TLR). Imaging follow-up includes duplex ultrasound imaging and stent radiographs at 6 and 12 months.

Results: This interim analysis includes 6-, 12-, and 24-month data from 742 patients (843 lesions), 592 patients (673 lesions), and 177 patients (221 lesions), respectively. The corresponding EFS rates were 95%, 87%, and
78%, and freedom from TLR rates were 96%, 89%, and 82%. Evaluation of stent radiographs is ongoing and currently suggests fractures in approximately 1.4% (21 of 1486) of stents at 6 months and 1.8% (21 of 1198) at 12 months. Clinical measures (ankle-brachial index, Rutherford score, walking distance, and speed scores) showed significant improvement, which was maintained through 24 months.

**Conclusions:** Interim results from the registry, including 2-year follow-up, indicate no safety concerns, low fracture rates, high rates of EFS and freedom from TLR, and clinical improvement with the DES. Ongoing registry follow-up, as well as the randomized study, will continue to evaluate the performance of the Silver® PTX™ Drug-Eluting Stent.

**Commentary LB2:** The investigators report interim nonrandomized registry data describing the use of drug-eluting stents in femoropopliteal disease. Generally favorable rates of event-free survival, freedom from target lesion revascularization, and clinical improvement are achieved. As with all registries, the absence of comparative groups limits the strength of any conclusions. Information from the randomized trial is pending. Most participants were limited to 1-year follow-up, and questions remain about how this relates to the duration of localized drug delivery with these drug-eluting stents. How long will any drug delivery effect be expected to last?

This area continues to be explored, and the performance of these stents needs to be compared with other interventions, including nondrug-eluting stents, and an exercise/medical therapy approach. Until then, the role and benefit of drug-eluting stents in peripheral artery disease remains unclear.

**LB3. Five-Year Outcomes of the Medtronic Talent AAA Stent-Graft Pivotal IDE Trial.** Sanchez LA; for the Talent eLPS IDE Trial Investigators.

**Objectives:** The Talent Enhanced Low Profile (eLPS) Trial led to the approval of the Talent abdominal aortic aneurysm (AAA) stent graft in the United States (US). The objective was to demonstrate the acute and long-term safety and effectiveness of endovascular aneurysm repair (EVAR) using the Talent graft. At 1 year, stent graft outcomes were compared with open surgery historical controls from the Society of Vascular Surgery (SVS) Lifeline IDE (investigational device exemption) Registry.

**Methods:** Between February 2002 and April 2003, 166 patients (91.6% men; mean age, 74.1 years) received the Talent graft at 13 US centers. Inclusion criteria included an AAA ≥4.0 cm in diameter and a proximal neck length of >5 mm with a diameter of >14 mm and <32 mm. Postprocedural evaluation involved plain x-ray films and computed tomography angiography before discharge, at 30 days, 1 year, and yearly to 5 years. Data from the SVS open repair IDE registry contained comparable data for 243 patients (81.5% men; mean age, 70.1 years) out to 1 year. Aneurysm-related mortality (ARM) was defined as death that occurred ≤1 month of the index procedure to treat the AAA, from AAA rupture, or from any procedure intended to treat the AAA.

**Results:** The EVAR population was older and sicker than the open repair population, with higher rates of arrhythmia (44.0% vs 11.5%), congestive heart failure (28.3% vs 4.9%), hypertension (83.7% vs 66.7%), and peripheral vascular disease (46.4% vs 15.6%). EVAR was superior to open repair for all perioperative outcomes: mean procedure duration (167.3 vs 196.4 minutes, P < .001), blood transfusion (18.2% vs 56.8%, P < .001), median intensive care unit stay (19.3 vs 74.3 hours, P < .001), and mean hospital stay (3.6 vs 8.2 days, P < .001). Freedom from major adverse events was better for EVAR at 30 days (89.2% vs 44.0%, P < .001) and 1 year (81.3% vs 42.4%, P < .001). Freedom from ARM was superior for EVAR at 1 year (98.2% vs 96.7%) and was 96.5% for EVAR at 5 years. Freedom from aneurysm rupture was 98.2%, and conversion to surgery was 99.1% at 5 years. The core laboratory reported one device migration at 1 year, and the sites reported four additional migrations between 2 and 5 years; 1 required a secondary procedure. A total of 28 new and persistent type I and III endoleaks were reported through 5 years; 9 required a secondary procedure.

**Conclusion:** The Talent eLPS Pivotal trial showed excellent safety and effectiveness compared with open surgical repair at 1 year. Durability and effectiveness of EVAR is maintained to 5 years. ARM at 5 years was low in a population that included patients with more challenging anatomic characteristics than other AAA IDE trials.

**Commentary LB3:** These investigators report the 5-year follow-up results of the initial Medtronic Talent AAA IDE Study and compare outcomes with those from the SVS Lifeline Registry open surgical controls. The anatomic inclusion criteria allowed for less optimal aortic anatomy (neck length >5 mm) for EVAR compared with other AAA IDE trials, with 34% of patients having proximal neck lengths <15 mm and diameters >28 mm.

Despite this challenging anatomy, there were high rates of freedom from all-cause mortality (68.8%), freedom from ARM (96.5%), and low rates of endoleaks, graft migration, secondary procedures, and conversion to open repair at 5 years. These 5-year results compare favorably with those of other devices. The investigators have continued to add more patients to the VITALITY Post-Approval US Study to look at the longer-term safety and effectiveness.


**Objective:** To report the intermediate-term (24-month) outcomes of a prospective multicenter trial designed to evaluate the Zenith Fenestrated AAA (abdominal aortic aneurysm) Endovascular Graft for treating juxtarenal AAAs.

**Methods:** Six centers in the United States enrolled 30 patients with juxtarenal AAAs with ≥50 mm diameter and
short proximal necks. The aims of the study were to evaluate the safety and preliminary effectiveness of the device, assess the physician learning curve, refine patient selection criteria, and develop experienced physicians. Devices were custom-designed for each patient based on measurements from reconstructed computed tomography (CT) data. Follow-up included physical examinations, laboratory studies, CT imaging, mesenteric-renal duplex ultrasound, and kidneys ureter and bladder radiography at hospital discharge, at 1, 6, and 12 months, and yearly thereafter up to 5 years.

Results: During a 1-year period, 30 patients (80% men; mean age, 75 years; mean aneurysm size, 6.14 mm) were enrolled in whom 77 visceral vessels were accommodated by fenestrations located within the sealing segment of the grafts. The most common design accommodated two renal arteries and the superior mesenteric artery (66.7%). All prostheses were implanted successfully without any acute loss of visceral arteries. Of the 30 patients treated, follow-up was available for 27 at 12 months and 23 at 24 months. No aneurysm-related deaths, aneurysm ruptures, or conversions were observed through 24 months of follow-up. No type I or type III endoleaks were observed at any time. Type II endoleaks were noted in 26.1% (6 of 23) at 12 months and in 20.0% (4 of 20) at 24 months. No aneurysm growth >5 mm occurred. Aneurysm size decreased in 69.6% (16 of 23) and was stable in the remaining patients at 24 months. Eight patients experienced evidence of some renal event (4 renal artery stenoses, 2 renal artery occlusions, and 2 renal infarcts), and among them, 5 underwent secondary interventions. No renal failure developed requiring dialysis.

Conclusions: The placement of fenestrated endovascular grafts is feasible at centers with experience in endovascular aneurysm repair and renal/mesenteric stent placement. The intermediate-term (24-month) results are concordant with other studies at single centers and support the concept that this technology is safe, effective, and transferable across multiple centers.

Commentary LB4: The infrarenal aorta continues to dilate after standard infrarenal endograft placement, making the proximal seal in a short neck tenuous at best. An endovascular solution to this problem involves moving this attachment site cephalad to a more stable visceral aortic segment. The price to pay for this healthier aorta is a more complex procedure and the risk of adverse renal and visceral artery events. Such a renal event occurred in 8 of 30 patients in the present study, a somewhat higher rate than previous studies. The optimal visceral artery stent has yet to be determined.

The true value of such an approach will require longer follow-up beyond 2 years to see how durable this more proximal seal is, although early to midterm results in selected patients and selected experienced surgeons hands are encouraging. This approach appears transferable to suitably experienced surgeons and is an option for higher-risk patients with short infrarenal necks. Open repair remains a valid alternative in lower-risk individuals.


Objective: Although repair of large abdominal aortic aneurysms is well accepted, randomized clinical trials have failed to demonstrate benefit for early surgical repair of small aneurysms over surveillance. Endovascular repair has been demonstrated to be safer than open surgical repair in patients with large aneurysms, prompting a randomized trial of early endovascular repair vs surveillance in patients with small aneurysms.

Methods: Patients with 4- to 5-cm abdominal aortic aneurysms were randomized to early endovascular repair or ultrasound surveillance. Rupture or aneurysm-related death and overall death were compared in the two groups during a mean follow-up of 20 ± 12 (SD) months.

Results: Of 728 patients with small aneurysms (diameter, 4.5 ± 0.3 cm) 366 were randomly assigned to early endovascular repair and or 362 to ultrasound surveillance. The mean age was 71 ± 8 years, and approximately 13% were women. After mean follow up of 20 ± 12 months (range, 0-41 months), there were 15 deaths in each group (4.1%), and the unadjusted hazard ratio for mortality after early endovascular repair was 1.01 (95% confidence limit [CL] 0.49, 2.07; P = .98). Aneurysm rupture or aneurysm-related death occurred in two patients in each group (0.6%). The unadjusted hazard ratio was 0.99 (95% CL, 0.14, 7.06; P = .99) for early endovascular repair.

Conclusions: Early treatment with endovascular repair and vigorous ultrasound surveillance both appear to be safe alternatives for patients with small abdominal aneurysms, protecting the patient from rupture or aneurysm-related death for up to 3 years.

Commentary LB5: Randomized studies have failed to show an advantage to early open repair over surveillance of small aneurysms. The investigators postulated that there might be an advantage to early endovascular repair with its lower risk of perioperative mortality. Because the enrollment rates were slower than expected, the investigators performed a futility analysis of early results and decided to stop enrollment in November 2008, with 728 of the original 1050 patients recruited.

With no difference in aneurysm-related mortality, rupture, or survival, there does not appear to be an advantage to early endovascular repair over surveillance. During the 3-year follow-up period, however, 31% of the surveillance group underwent aneurysm repair, whereas 12% of the repair arm did not. This is important to keep in mind as the study follow-up is completed.

Objective: This research aimed to define relationships between iron storage and inflammatory biomarkers in co-hort of 100 participants at the Veterans Affairs (VA) Sierra Nevada Health Care System (SNHCS) with peripheral arterial disease (PAD). A prospective randomized, single, blind clinical trial entering 1277 cancer-free patients with advanced peripheral arterial disease (PAD) from 24 participating VA hospitals (VA Cooperative Study #410, The Iron and Atherosclerosis Study [FeAST]) tested the hypothesis that iron in excess of physiologic requirements contributes to atherosclerosis. Patients were randomized to calibrated iron reduction by graded phlebotomy or control groups. The primary outcome was all-cause mortality, and the secondary outcome was death plus nonfatal myocardial infarction and stroke. Data on cardiovascular disease (CVD) outcomes and on the occurrence of new cancer diagnoses and cancer-specific death were collected prospectively and analyzed by intent-to-treat. In the main study population, iron reduction resulted in a significant age-related improvement in primary and secondary CVD as well as cancer death. Levels of ferritin correlated with inflammatory biomarkers during the SNHCS substudy.

Methods: Approval was obtained to measure the cytokines interleukin (IL) 6, tumor necrosis factor-α receptors 1 and 2, IL-2, IL-10, and high-sensitivity C-reactive protein (hs CRP) at entry and at 6-monthly follow-up intervals on 100 participants monitored during the 6-year study period. We explored relationships between iron status (ferritin levels) and inflammatory markers at entry and during follow-up in this subset of FeAST participants.

Results: The main and substudy participants were an average age of 67 ± 9 years at entry. Clinical and laboratory parameters at entry were comparable in the 51 participants randomized to iron reduction and 49 controls. At baseline, 53 entrants receiving statins trended lower mean ferritin levels (114.06 ng/mL; 95% confidence interval [CI], 93.43-134.69) compared with 47 participants not receiving statins (127.6 ng/mL; 95% CI, 103.21-152.02; P = NS). During the study interval, 31 additional participants started taking statins. Longitudinal analysis using all follow-up data showed that after adjusting for the phlebotomy treatment effect, statins had a significant effect on the reduction of ferritin (−29.78 ng/mL), with a Cohen effect size of −0.47 (t = 2.33, P = .0123). Mean follow-up ferritin levels were higher in 23 participants who died compared with the 77 survivors (152 vs 86.3 ng/mL; P = .0050). Mean follow-up IL-6 levels were higher in the 23 participants who died compared with the 77 survivors (P = .03). Pearson correlations showed significant relationships between levels of ferritin and IL-6 (P = .002) and hsCRP (P = .04).

Conclusion: These data support the hypothesis that iron-catalyzed oxidative stress may contribute to inflammation in patients with PAD.

Commentary LB6: Important results from this VA study include the finding that higher ferritin levels and inflammatory biomarkers are associated with cardiovascular death and that statins reduced these ferritin levels, independent from the effects of phlebotomy. The investigators propose additional trials of iron reduction in younger patients and, in the mean time, continued statin use and consideration of iron reduction in those at risk of cardiovascular events.


Objectives: The evaluation of new devices targeting the critical limb ischemia (CLI) population presents major challenges in clinical trial design. We sought to develop objective performance goals (OPG) and to define appropriate outcome measures for CLI trials.

Methods: We pooled line-item data from three prospective multicenter trials of open surgical revascularization for CLI: Edifoligide for the Prevention of Infraplainguinal Vein Graft Failure (PREVENT-III), Circulase II, and By-pass versus Angioplasty in Severe Ischemia of the Leg (BASIL). We included data for patients undergoing surgical bypass using autogenous vein. Test-drug treatment, use of prosthetic, and end-stage renal disease patients were excluded. End points included major adverse cardiac events (MACE), death, amputation, and reintervention. We defined a major adverse limb event (MALE) as consisting of amputation or a major reintervention (new bypass graft, thrombolysis, jump or interpolation graft revision). Perioperative (30-day) death was combined with any MALE to generate the primary efficacy end point MALE(+). Other composite end points included amputation-free survival. Event rates were calculated by Kaplan-Meier analysis. Univariate and multivariate analyses defined risk criteria based on patient characteristics, anatomy, and conduit quality.

Results: Data from 838 surgical cases from the three trials were included. Perioperative MACE was 6.2%, including 2.7% mortality. The combination of age >80 years and tissue loss (80+) was associated with a 3.1-fold increased risk of 30-day MACE and notably inferior outcomes for all end points that included death as an event (Table). Infrapopliteal outflow anatomy and the use of a high-risk conduit (nonsaphenous, spliced, or small-caliber vein) were also significant outcome stratifiers, particularly for the limb-related end points.

Conclusions: Patient age (>80 years), presence of tissue loss, infrapopliteal disease, and lack of adequate saphenous vein are useful stratification criteria for clinical trial designs in the CLI population. MALE is a clinically relevant efficacy measure for limb revascularization, distinct from amputation-free survival. These data were used to
develop risk stratified OPG for catheter-based devices targeting CLI.

**Commentary LB7:** Any studies describing critical limb ischemia (CLI) are plagued with inconsistent definitions and use of outcome measures and reporting standards. In this Society for Vascular Surgery initiative, the authors attempt to clarify some of these issues regarding CLI outcome measures by pooling data from three recent trials. Elderly patients with tissue loss were more apt to experience a cardiac event or die, and suboptimal conduits and tibial disease were associated with more frequent limb-related events. These findings are not surprising. The main benefit of this study is the justification of a clinically relevant outcome measure, major adverse limb event (MALE), distinct from amputation-free survival. This allows for the setting of performance goals and use of such measures in further surgical revascularization and interventional CLI studies. The investigators propose an assessment schedule and a set of periprocedural and longer-term end points to be used in future CLI trials.


**Objectives:** We have previously reported the results of a dose-finding phase II trial showing that HGF angiogenic gene therapy can increase transcutaneous partial pressure of oxygen (TcPO₂) compared with placebo in patients with critical limb ischemia (CLI). This randomized, placebo-controlled, multicenter trial further assessed the safety and clinical efficacy of a modified HGF gene delivery technique in patients with CLI and no revascularization options.

**Methods:** Patients with tissue loss received three sets of eight intramuscular injections every 2 weeks of HGF plasmid under duplex ultrasound guidance. Injection locations were individualized for each patient based on arterio-graphically defined vascular anatomy. The primary safety end point was incidence of adverse events or serious adverse events. Clinical end points included change from baseline in toe-brachial index (TBI), rest pain assessment by a 10-cm visual analog scale, as well as wound healing, amputation, and survival at 3 and 6 months.

**Results:** The randomization ratio was 4:1 HGF (n = 21) vs placebo (n = 6). Mean age was 76 ± 2 years, 56% were men, and 59% were diabetic. There was no difference in demographics between groups. There was no difference in adverse events or serious adverse events, which consisted mostly of transient injection site discomfort, worsening of CLI, and intercurrent illnesses. Change in TBI and rest pain significantly improved from baseline at 6 months in the HGF-treated group compared with placebo (Table). Complete ulcer healing at 12 months occurred in 31% of the HGF group and in 0% of the placebo group (P = .21). There was no difference in amputation (HGF, 19% vs placebo, 20%) or mortality (HGF, 19% vs placebo, 13%) between groups.

**Conclusions:** HGF gene therapy using a patient vascular anatomy specific delivery technique appears safe, maintained limb perfusion, and decreased rest pain in patients with CLI compared with placebo. A larger study to assess the efficacy of this therapy on more clinically relevant end points is warranted.

**Commentary LB8:** The investigators report promising results after HGF angiogenic gene therapy, with improvements in toe-brachial indices, pain control, and ulcer healing in a small cohort (n = 21) of patients with tissue loss compared with placebo (n = 6). Amputation rates did not differ. Injection sites in the ischemic extremity were individualized and guided based on the anatomic distribution of the occlusive disease. As larger studies are performed to validate these results, it will be interesting to correlate revascularization and limb salvage outcomes with the local effects of these injections on the peripheral vasculature.

**Table. Study outcomes**

<table>
<thead>
<tr>
<th>Outcome by group</th>
<th>3 months</th>
<th>P</th>
<th>6 months</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete ulcer healing, %</td>
<td>HGF 6%</td>
<td>1.0</td>
<td>19%</td>
<td>.55</td>
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<tr>
<td>Placebo 0%</td>
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<td></td>
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<tr>
<td>Difference from baseline</td>
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<tr>
<td>Visual analog pain score (cm)</td>
<td>HGF -1.05 ± 0.8</td>
<td>.20</td>
<td>-1.91 ± 1.3</td>
<td>.04</td>
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<tr>
<td>Placebo 0.5 ± 0.3</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toe pressure</td>
<td>HGF 6.8 ± 5.8</td>
<td>.02</td>
<td>5.8 ± 6.9</td>
<td>.07</td>
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<tr>
<td>Placebo -25 ± 2.0</td>
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<tr>
<td>Toe-brachial index</td>
<td>HGF 0.04 ± 0.04</td>
<td>.057</td>
<td>0.05 ± 0.05</td>
<td>.047</td>
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<tr>
<td>Placebo -0.14 ± 0.02</td>
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