LIBERTY 360° Study

LIBERTY is a prospective, observational, multi-center study to evaluate procedural and long-term clinical and economic outcomes of endovascular device interventions in patients with symptomatic lower extremity peripheral artery disease (PAD).

PAD PROGNOSIS
- For intermittent claudication (IC) patients, over a 5-year period, significant deterioration appears in 20% of cases, of whom 2/3 with worsening claudication and 1/3 with Critical Limb Ischemia (CLI). For CLI patients, after 1-year, mortality is 20%, amputations are needed in 30%, while 45% are alive with both legs intact.¹

STUDY DESIGN
- The LIBERTY study includes any FDA-approved technology to treat claudication and CLI.
- Lesions studied were within or extending into 10 cm above the medial epicondyle to the digital arteries (distal 1/3 of the SFA and below).
- 4 core laboratories were utilized for independent analysis.
- 1204 subjects were enrolled at 51 sites spanning a broad spectrum of sites of care including community hospitals, large teaching hospitals, VA centers, and office-based labs (OBLs).
- 131 operators treated patients in LIBERTY; 37 individual operators treated RC6 patients.
- Endpoints include: Procedural and lesion success, Major Adverse Events (MAEs), Duplex ultrasound, Quality of Life (QoL), Six-minute walk test (6MWT), Economic analysis.

KEY TAKEAWAYS
- The findings in this novel, all-comers, 1,200-patient PAD study demonstrated high freedom from major amputation at 2 years and in an OAS sub-analysis despite complex demographics.
- Freedom from 2-year target vessel revascularization (TVR)/target lesion revascularization (TLR) rates are similar in RC4-5 and RC6.
- Significant improvement through 2 years in: Rutherford Class (RC) in all groups; Patient reported quality of life in all groups; Number of wounds in RC4-5 and RC6.
- 2-year MAE predictor model indicates that many traditional predictors are significant in an unadjusted model yet when accounting for potential covariates, those associated with disease progression and previous treatments were most strongly correlated with 2-year MAE.
- Peripheral vascular intervention (PVI) is a reasonable treatment option for RC2-3 and RC4-5.
- Primary amputation may not be necessary in RC6—PVI can be successful in this patient population, as evidenced at 2 years by high freedom from major amputation (79.8%) and improvement in QoL and RC.

¹ 15-Jun-2018 Data
### PATIENT POPULATION

**ENROLLMENT AND 2-YEAR FOLLOW-UP**

1204 Subjects Enrolled at 51 sites
- All Comers / All Treatments

- **Rutherford 2-3**
  - 500 Subjects*
  - 605 Lesions
  - 333 Subjects
  - 19.4% withdrawal/lost to follow-up
  - 6.2% missed 2-year visit
  - 8.0% died

- **Rutherford 4-5**
  - 589 Subjects*
  - 775 Lesions
  - 320 Subjects
  - 28.7% withdrawal/lost to follow-up
  - 6.1% missed 2-year visit
  - 12.1% died

- **Rutherford 6**
  - 100 Subjects
  - 148 Lesions
  - 31 Subjects
  - 34.0% withdrawal/lost to follow-up
  - 10.0% missed 2-year visit
  - 25.0% died

*Due to site closure and lack of PI signature, baseline and procedure data from 15 subjects were excluded.

Rutherford 2, N=97; Rutherford 3, N=403; Rutherford 4, N=285; Rutherford 5, N=304. Core Lab reported lesions.

### KEY LIBERTY LESION CHARACTERISTICS

*High number of chronic total occlusions (CTOs) and below-the-knee (BTK) lesions treated across all groups.*

<table>
<thead>
<tr>
<th>Subject Lesion Characteristics</th>
<th>RC2-3 (N=500)</th>
<th>RC4-5 (N=589)</th>
<th>RC2-6 (N=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of lesions treated</td>
<td>1.2 ± 0.5</td>
<td>1.3 ± 0.6</td>
<td>1.5 ± 0.7</td>
</tr>
<tr>
<td></td>
<td>N=497</td>
<td>N=588</td>
<td>N=99</td>
</tr>
<tr>
<td>Chronic total occlusions</td>
<td>181 (37.3%)</td>
<td>307 (53.1%)</td>
<td>50 (51.5%)</td>
</tr>
<tr>
<td></td>
<td>N=485</td>
<td>N=578</td>
<td>N=97</td>
</tr>
<tr>
<td>Mean target lesion length</td>
<td>10.7 ± 9.9</td>
<td>17.0 ± 13.7</td>
<td>15.3 ± 12.2</td>
</tr>
<tr>
<td></td>
<td>(N=464)</td>
<td>(N=563)</td>
<td>(N=95)</td>
</tr>
<tr>
<td>Location of all lesions treated</td>
<td>N=497</td>
<td>N=587</td>
<td>N=98</td>
</tr>
<tr>
<td>Above-the-knee (ATK) only</td>
<td>238 (47.9%)</td>
<td>130 (22.1%)</td>
<td>24 (24.5%)</td>
</tr>
<tr>
<td>ATK and BTK</td>
<td>120 (24.1%)</td>
<td>164 (27.9%)</td>
<td>28 (28.6%)</td>
</tr>
<tr>
<td>BTK only</td>
<td>139 (28.0%)</td>
<td>293 (49.9%)</td>
<td>46 (46.9%)</td>
</tr>
</tbody>
</table>

N (%) or Mean ± SD as appropriate.
Core Lab reported lesions (Lesions with reported values may be less than total number of lesions treated in each arm).
STUDY RESULTS

TOTAL OUTCOMES THROUGH 2 YEARS BY RUTHERFORD CLASS

**FF MAE: RC2-3 74.7%  RC4-5 65.6%  RC6 50.9%**

**FF - Major Amputation**
- RC2-3: 99.1%
- RC4-5: 94.5%
- RC6: 79.8%

**FF - TVR/TLR**
- RC2-3: 75.2%
- RC4-5: 67.8%
- RC6: 65.7%

**FF - Death†**
- RC2-3: 91.4%
- RC4-5: 85.7%
- RC6: 71.5%

Despite complex demographics (e.g. history of lower extremity PVI, history of myocardial infarction (MI), CTOs, lesion length) in this real-world study, there was high freedom from (FF) major amputation at 2 years in RC2-3 (99.1%), RC4-5 (94.5%), and RC6 (79.8%) and similar freedom from 2-Year TVR/TLR rates in RC4-5 (67.8%) and RC6 (65.7%).

Kaplan-Meier method used to obtain estimate rates. Greenwood’s method used to obtain the 95% confidence interval for the estimate.

†All-Cause Death rate shown here is at 2 years, but the Freedom from MAE only includes death within 30-days of the procedure.

OAS SUBANALYSIS: OUTCOMES THROUGH 2 YEARS BY RUTHERFORD CLASS

**FF MAE: RC2-3 77.8%  RC4-5 68.0%  RC6 61.3%**

**FF - Major Amputation**
- RC2-3: 100%
- RC4-5: 95.3%
- RC6: 88.5%

**FF - TVR/TLR**
- RC2-3: 78.6%
- RC4-5: 71.1%
- RC6: 70.7%

**FF - Death†**
- RC2-3: 90.7%
- RC4-5: 84.1%
- RC6: 75.5%

OAS was the most frequently used atherectomy device. High freedom from (FF) major amputation in all Rutherford Classes (RC2-3, 100%; RC4-5, 95.3%; and RC6, 88.5%). Similar rates of freedom from TVR/TLR were seen across all Rutherford Classes.

Kaplan-Meier method used to obtain estimate rates. Greenwood’s method used to obtain the 95% confidence interval for the estimate.

†All-Cause Death rate shown here is at 2 years, but the Freedom from MAE only includes death within 30-days of the procedure.
SIGNIFICANT IMPROVEMENT IN RUTHERFORD CLASS FROM BASELINE TO 2 YEARS IN ALL GROUPS.

QUALITY OF LIFE IMPROVED SIGNIFICANTLY FROM BASELINE TO 2 YEARS IN ALL RUTHERFORD CLASSES.

Vascular Quality of Life Questionnaire; a PAD-specific health-related quality of life instrument. Higher subdomain scores indicate better rating of health.

Mean Total Score differences assessed via paired t-test.
TARGET LIMB WOUND HEALING

CLI patients showed continued improvement in number of wounds from 30 days to 2 years.

2-YEAR OUTCOMES PREDICTOR ANALYSIS

RUTHERFORD CATEGORY IS A PREDICTOR OF MAJOR AMPUTATION AND ALL-CAUSE DEATH. NUMBER OF WOUNDS ON TARGET LIMB AT BASELINE IS THE ONLY CONSISTENT PREDICTOR FOR ALL 24-MONTH OUTCOMES ASSESSED ILLUSTRATING THE IMPORTANCE OF EARLY DETECTION AND TREATMENT, AS WELL AS PROPER WOUND CARE.

<table>
<thead>
<tr>
<th>Rutherford Classification</th>
<th>RC2-3</th>
<th>RC4-5</th>
<th>RC6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with wound data at 2 years</td>
<td>312</td>
<td>299</td>
<td>25</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.03 ± 0.26</td>
<td>0.13 ± 0.49</td>
<td>0.24 ± 0.83</td>
</tr>
</tbody>
</table>

2-YEAR OUTCOMES PREDICTOR ANALYSIS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Major Adverse Events</th>
<th>Target Vessel Revascularization</th>
<th>Major Amputation</th>
<th>All-Cause Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rutherford category</td>
<td>Adjusted Hazard Ratio (95% CI)</td>
<td>P-value</td>
<td>Adjusted Hazard Ratio (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Age (1 year increase)</td>
<td>1.31 (1.02, 1.69)</td>
<td>0.037</td>
<td>1.74 (1.35, 2.24)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>History of MI</td>
<td>1.31 (1.02, 1.69)</td>
<td>0.037</td>
<td>1.74 (1.35, 2.24)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>History of renal disease</td>
<td>1.31 (1.02, 1.69)</td>
<td>0.037</td>
<td>1.74 (1.35, 2.24)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>History of previous lower extremity peripheral vascular interventions for PAD</td>
<td>1.68 (1.31, 2.14)</td>
<td>&lt;0.001</td>
<td>1.74 (1.35, 2.24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of target limb procedures in the last 3 yrs (1 proc. increase)</td>
<td>1.09 (1.03, 1.14)</td>
<td>0.001</td>
<td>1.09 (1.03, 1.14)</td>
<td>0.001</td>
</tr>
<tr>
<td>Previous major amputation on non target limb (above ankle)</td>
<td>1.75 (1.10, 2.79)</td>
<td>0.018</td>
<td>1.75 (1.10, 2.79)</td>
<td>0.018</td>
</tr>
<tr>
<td>Number of wounds on target limb at baseline (1 unit increase)</td>
<td>1.31 (1.18, 1.46)</td>
<td>&lt;0.001</td>
<td>1.25 (1.11, 1.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic total occlusions (At least 1 vs 0)</td>
<td>1.92 (1.48, 2.49)</td>
<td>&lt;0.001</td>
<td>2.30 (1.81, 2.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total treated lesion length (cm, 1 unit increase)</td>
<td>1.01 (1.00, 1.02)</td>
<td>0.045</td>
<td>1.01 (1.00, 1.02)</td>
<td>0.045</td>
</tr>
<tr>
<td>Distal treated region</td>
<td>NA</td>
<td>0.005</td>
<td>NA</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*RC4-5 vs. 6, and RC2-3 vs. 6 are significant (p<0.05) when using contrast to estimate Hazard ratio between 2 levels of Rutherford category. Additional variables included in the model (not listed in above table): gender, BMI, race, ethnicity, history of stroke/TIA, history of hypertension, history of hyperlipidemia, history of smoking, history of diabetes, history of coronary artery disease, number of core lab reported lesions, predominant calcified plaque morphology, most severe PARC calcification grade, most severe TASC lesion type, bailout stent use, <50% residual stenosis on all lesions post-procedure, subject had significant angiographic complication. Predictors determined from Cox proportional hazard regression using stepwise selection. P-values based on Wald test; however a Type 3 test was used for categorical variables. Covariates found significant in a univariable model with an alpha of 0.1 were placed into a multivariable model; final multivariable model was created using stepwise selection with an entry criteria of 0.15 and a stay criteria of 0.05.
PROCEDURAL OUTCOMES

- High procedural lesion treatment success across all RCs at 2 years (RC2–3: 84%, RC4–5: 76%, RC6: 69%).
- One of the first procedural and lesion outcome datasets on RC6 patients. In this study, PVI in RC6 subjects resulted in <50% residual stenosis in 83% of the lesions treated, no severe angiographic complications in 88% of lesions.
- Procedural complications rarely (0.8%-2.0%) resulted in post-procedural hospitalization in all RCs and 78% of RC6 subjects were discharged to home.
- Improvement in outflow distal to the treated vessel(s) in 16% of RC2-3, 32% of RC4-5, and 39% of RC6 post-PVI. Worsened outflow was seen in less than 2% of CLI patients post-PVI.

2-YEAR OUTCOMES

- High freedom from major amputation at 2 years in RC2-3 (99.1%), RC4-5 (94.5%), and RC6 (79.8%) and in an OAS sub-analysis in RC2-3 (100%), RC4-5 (95.3%), and RC6 (88.5%) despite complex demographics.
- Freedom from 2-year TVR/TLR rates are similar in RC4-5 (67.8%) and RC6 (65.7%).
- Significant improvement through 2 years in:
  - Rutherford Class in all groups;
  - Patient reported quality of life in all groups;
  - Number of wounds in RC4-5 and RC6.
- 2-year MAE predictor model indicates that many traditional predictors are significant in an unadjusted model, yet when accounting for potential covariates, those associated with disease progression and previous treatments were most strongly correlated with 2-year MAE.