Randomized trial comparing cyanoacrylate embolization and radiofrequency ablation for incompetent great saphenous vein

Raghu Kolluri, MD,
Director – Vascular Medicine
OhioHealth | Riverside Methodist Hospital
Columbus, OH
Disclosures

- **Current**
  - Medtronic – Consultant/ Speaker
  - Bard – Data Safety Committee
  - Cook – Consultant
  - Volcano – Consultant
  - Boston Scientific – Consultant/ Speaker
# Adhesives in Medicine

<table>
<thead>
<tr>
<th>Adhesives</th>
<th>Date</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyanoacrylate Adhesives</td>
<td>1950s</td>
<td>Wound adhesives</td>
</tr>
<tr>
<td>Histoacryl Blue™ *</td>
<td>1980s</td>
<td>Skin incisions</td>
</tr>
<tr>
<td>Dermabond™ *</td>
<td>1998</td>
<td>Skin incisions/ lacerations</td>
</tr>
<tr>
<td>Ethicon OMNEX™ *</td>
<td>1998</td>
<td>Surgical adhesives</td>
</tr>
<tr>
<td>Trufill™ *</td>
<td>2000</td>
<td>Liquid Embolic System, AVM embolization</td>
</tr>
<tr>
<td>Indermil™ *</td>
<td>2002</td>
<td>Skin incisions/ lacerations</td>
</tr>
</tbody>
</table>

Cyanoacrylate Use in vascular

Vascular closing agent for:

- Cerebral Arteriovenous malformations (AVM)
- Pelvic congestion syndrome and Varicoceles
- Gastric varices
- Aortic aneurysms
VenaSeal™ Closure System

CYANOCRYLATE ADHESIVE TO CLOSE THE DISEASED VEIN

- Proprietary formulation of advanced medical cyanoacrylate-based adhesive
- Proprietary catheter engineered to be inert to adhesive – “doesn’t stick”
- Proprietary dispenser gun designed to deliver adhesive precisely
Properties of Ideal Cyanoacrylate for Venous Closure

- Ideal viscosity
- Polymerize quickly
- Soft and elastic (dynamic part of body)
- Maintains a strong bond
**PROCEDURE**

- **VenaSeal™ Closure System**
- **Access GSV using catheter**
- **Position catheter 5 cm from SFJ**
- **Compress cephalad to catheter**
VenaSeal™ Closure System

PROCEDURE

Inject 0.10 cc adhesive into the vein, pull back 1 cm, inject 0.10 cc pull back 3 cm

Compress 3 minutes

Inject 0.10 cc, pull back 3 cm, compress for 30 seconds

Repeat process throughout vein
Ultrasound Images 8 weeks post treatment

VenaSeal™ Procedure Closure

RFA Procedure Closure

Images courtesy of Dr. R. Raabe
Clinical Studies with VenaSeal™ System

Feasibility Study
- 38 Patients, enrollment completed August 2011
- 1, 3, 6, 12, 24 and 36 month follow-ups
- **Primary endpoint**: Safety: rate of serious adverse events,
  **Efficacy**: vein closure during follow-up

eSCOPE
*(European multicenter study)*
- 70 patients, enrollment completed September 2012
- 2 day, 1, 3, 6, 12, 24 and 36 month follow-ups
- **Primary endpoint**: closure w/o use of sedation, tumescent anesthesia, or compression stockings

VeClose
*(U.S. pivotal trial)*
- 242 patients, enrollment completed September 2013
- 3 day, 1, 3, 6, 12 months & 2, 3 year follow-ups
- **Primary endpoint**: non-inferior to RFA in GSV closure
- **Secondary endpoint**: superiority in reduction of post procedural pain and bruising
# Feasibility Study Results

## FOLLOW-UP THROUGH 36-MONTHS

<table>
<thead>
<tr>
<th>Sample Size</th>
<th>Rate of Occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Year(^1)</td>
<td>N=36 92%</td>
</tr>
<tr>
<td>2-Year(^2)</td>
<td>N=29 92%</td>
</tr>
<tr>
<td>3-Year(^3)</td>
<td>N=29 92%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sample Size</th>
<th>VCSS Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>N=38 6.1</td>
</tr>
<tr>
<td>1-Year(^1)</td>
<td>N=36 1.5</td>
</tr>
<tr>
<td>2-Year(^3)</td>
<td>N=29 2.5</td>
</tr>
<tr>
<td>3-Year(^3)</td>
<td>N=29 2.2</td>
</tr>
</tbody>
</table>

\(^3\)Almeida J. Three-year follow-up of first human use of cyanoacrylate adhesive for treatment of saphenous vein incompetence. AVF 2015
Prospective, non-randomized, multicenter study
To evaluate safety, efficacy of the VenaSeal™ closure system for the treatment of refluxing great saphenous veins
70 patients enrolled
Follow-up assessments at 48 hours, 1, 3, 6, 12, 24 and 36 months

Duplex ultrasound closure without use of sedation, tumescent anesthesia or compression stockings

No adjunctive treatments for 3 months

**eSCOPE Study- Results**

**FOLLOW-UP THROUGH 12-MONTHS**

<table>
<thead>
<tr>
<th>Follow-up Time</th>
<th>Rate of Occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-Month</td>
<td>94.3%</td>
</tr>
<tr>
<td>12-Month</td>
<td>92.9%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Mean VCSS Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>4.3</td>
</tr>
<tr>
<td>12-Month</td>
<td>1.1</td>
</tr>
</tbody>
</table>

VeClose

U.S. PIVOTAL TRIAL

**Study Design**
- Prospective, randomized 1:1 comparing VenaSeal™ system (VS) to RFA (ClosureFast™ catheter).

**Purpose**
- Demonstrate safety and effectiveness of the VenaSeal™ closure system (VSCS) for the treatment of lower extremity truncal reflux by showing non-inferiority at three months to RFA using the ClosureFast™ system.

**Subjects**
- 242 patients were enrolled
- 20 Roll-in/Training on VSCS, the rest randomized to
- 108 VSCS, 114 RFA = Randomized Cohort

VeClose (U.S. PIVOTAL TRIAL)

Primary Endpoint
- Duplex ultrasound determined closure of the GSV, non-inferiority of VenaSeal™ closure system to RFA with the ClosureFast™ catheter

Secondary Endpoints
- Intraoperative pain, rated on a 0-10 numeric rating scale
- Ecchymosis at day 3, rated on a 0-5 ordinal scale
- Adverse events at 1 month

Follow-up occurred at
- Day 3, and
- 1, 6 and 12 months post-procedure & 2, 3 year follow ups

No adjunctive therapy before 3 months

Follow-up Compliance Through 12-Months

190 Subjects completed the 12-month visit

222 Subjects Randomized (1:1) and Treated

VSCS N=108

1-Month Follow-up Compliance N=105
3-Month Follow-up Compliance N=104
6-Month Follow-up Compliance N=101
12-Month Follow-up Compliance N=95

RFA N=114

1-Month Follow-up Compliance N=110
3-Month Follow-up Compliance N=108
6-Month Follow-up Compliance N=104
12-Month Follow-up Compliance N=95

Morrison N. Use Of Cyanoacrylate Adhesive For Treatment Of Incomplete Great Saphenous Veins: 12-month Results of the VeClose Trial. European Venous Forum. 2015
# VeClose Results

## BASELINE CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>VSCS (N=108)</th>
<th>RFA (N=114)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>49.0</td>
<td>50.5</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>Body Mass Index</strong></td>
<td>27.0</td>
<td>27.0</td>
<td>0.95</td>
</tr>
<tr>
<td><strong>Mean GSV diameter (mm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>6.3</td>
<td>6.6</td>
<td>0.15</td>
</tr>
<tr>
<td>Mid-thigh</td>
<td>4.9</td>
<td>5.1</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>Mean Treatment Length (cm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>32.8 (108)</td>
<td>35.1 (114)</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>Mean VCSS</strong></td>
<td>5.5 ± 2.6</td>
<td>5.6 ± 2.6</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>Mean AVVQ</strong></td>
<td>18.9 ± 9.0</td>
<td>19.4 ± 9.9</td>
<td>0.72</td>
</tr>
<tr>
<td><strong>Mean EQ-5D TTO</strong></td>
<td>0.935 ± 0.113</td>
<td>0.918 ± 0.116</td>
<td>0.29</td>
</tr>
</tbody>
</table>

VCSS: Venous Clinical Severity Score; AVVQ: Aberdeen Varicose Vein Questionnaire
# VeClose Results

## PROCEDURAL CHARACTERISTICS AND INTRAOPERATIVE PAIN

<table>
<thead>
<tr>
<th></th>
<th>VSCS (N=108)</th>
<th>RFA (N=114)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumescent Anesthesia Volume (mL)</td>
<td>Not applicable</td>
<td>272</td>
<td>-</td>
</tr>
<tr>
<td>Lidocaine Use During Procedure (mL)</td>
<td>1.6</td>
<td>2.7</td>
<td>0.1</td>
</tr>
<tr>
<td>Cyanoacrylate delivered, (mL)</td>
<td>1.2</td>
<td>Not applicable</td>
<td>-</td>
</tr>
<tr>
<td>Intraoperative pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During Vein Access</td>
<td>1.6</td>
<td>2.0</td>
<td>0.13</td>
</tr>
<tr>
<td>During Treatment</td>
<td>2.2</td>
<td>2.4</td>
<td>0.11</td>
</tr>
</tbody>
</table>
Ecchymosis assessed by investigators with a 5-point scale on Day 3.

Subjects treated with VenaSeal™ system had significantly less ecchymosis at Day 3 compared to RFA (p< 0.01 Wilcoxon test).
VeClose Complete Closure Definition

Sites and CoreLab

- Complete closure = Doppler ultrasound examination showing closure along entire treated target vein segment with no discrete segments of patency exceeding 5 cm.
- Ultrasound exams used 2D imaging, Color Doppler and Pulsed Doppler.
3 month closure data were adjudicated by an independent ultrasound core laboratory (VasCore)

*There was complete agreement between sites and the CoreLab. Both were blinded to the results from each other. Predictive method for imputing missing data was utilized for analysis.
VeClose Results

KAPLAN-MEIER ANALYSIS OF CLOSURE THROUGH 12-MONTHS

Closure Rate at 12-months

- VSCS: 97.2%
- RFA: 97.1%

Morrison N. Use Of Cyanoacrylate Adhesive For Treatment Of Incompetent Great Saphenous Veins: 12-month Results of the VeClose Trial. European Venous Forum. 2015
VeClose Results

TIME TO RECANALIZATION OF THE TARGET VEIN

Survival Free from Recanalization at 12-Months

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSCS</td>
<td>97.0%</td>
</tr>
<tr>
<td>RFA</td>
<td>91.7%</td>
</tr>
</tbody>
</table>

P<0.0001 for non-inferiority

Morrison N. Use Of Cyanoacrylate Adhesive For Treatment Of Incompetent Great Saphenous Veins: 12-month Results of the VeClose Trial. European Venous Forum. 2015
VeClose Results

VCSS MEAN & (SD) BY VISIT AND TREATMENT

VeClose Results

AVVQ MEAN & (SD) BY VISIT AND TREATMENT

VeClose Results

EQ-5D MEAN & (SD) BY VISIT AND TREATMENT

# VeClose Results

**ADVERSE EVENTS THROUGH 6 MONTHS**

*No serious AEs were categorized as device and/or procedure-related*

<table>
<thead>
<tr>
<th></th>
<th>VSCS (N=108)</th>
<th>RFA (N=114)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td># Subjects with events (%)</td>
<td>34 (31%)</td>
<td>29 (25%)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Reported AEs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phlebitis, any zone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phlebitis in treatment zone</td>
<td>22 (20.4%)</td>
<td>16 (14.0%)</td>
<td>0.3571</td>
</tr>
<tr>
<td>Phlebitis not in treatment zone</td>
<td>11 (10.2%)</td>
<td>10 (8.8%)</td>
<td>0.8199</td>
</tr>
<tr>
<td>Phlebitis in both treatment zone and non-treatment zone</td>
<td>8 (7.4%)</td>
<td>4 (3.5%)</td>
<td>0.2430</td>
</tr>
<tr>
<td>Phlebitis in both treatment zone and non-treatment zone</td>
<td>1 (0.9%)</td>
<td>1 (0.9%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Paresthesia in treatment zone</td>
<td>3 (2.8%)</td>
<td>3 (2.6%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Stocking irritation</td>
<td>2 (1.9%)</td>
<td>3 (2.6%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Access site infection</td>
<td>1 (0.9%)</td>
<td>1 (0.9%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Superficial thrombophlebitis</td>
<td>4 (3.7%)</td>
<td>3. (2.6%)</td>
<td>0.7157</td>
</tr>
<tr>
<td>Access site burn</td>
<td>0 (0%)</td>
<td>1 (0.9%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Paresthesia not in treatment zone</td>
<td>0 (0%)</td>
<td>1 (0.9%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Paresthesia in treatment zone</td>
<td>3 (2.8%)</td>
<td>3 (2.6%)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Morrison N. Use Of Cyanoacrylate Adhesive For Treatment Of Incompetent Great Saphenous Veins: 12-month Results of the VeClose Trial. European Venous Forum. 2015
Summary of Clinical Evidence with VenaSeal™ System

- The VenaSeal™ procedure is **safe and effective**, (three clinical trials)

- **High closure rate:** 92% in Feasibility study through 3 year follow-up, 92.9% at 12 months in eSCOPE study and 97.2% in VeClose trial at 12 months.

- **Acceptable safety profile:** Side effects are minor and infrequent.

- Use of the VenaSeal™ system does not require post procedure compression stockings as shown in FIH and eSCOPE studies.
Thank you
Randomized trial comparing cyanoacrylate embolization and radiofrequency ablation for incompetent great saphenous vein

Raghu Kolluri, MD,
Director – Vascular Medicine
OhioHealth | Riverside Methodist Hospital
Columbus, OH