Catheter-Directed Mechanical Thrombectomy for Intermediate-Risk Acute Pulmonary Embolism: The FLARE Study

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VEITH 2018
November 13, 2018

Disclosures

• Nothing to disclose

Background

- Catheter-directed thrombolysis (CDT) has been shown to improve right ventricular function in patients with acute pulmonary embolism (PE)
- However, prolonged ICU stay, need for thrombolytic administration, and potential bleeding complications with CDT therapy may limit its broad application
- Catheter-directed mechanical thrombectomy is an alternative approach that does not require the use of thrombolytics, but hasn't yet been widely evaluated for safety and efficacy

Increased RV/LV Ratio Is An Independent Predictor of PE-Related Mortality

Conclusion:

"Both RV strain on TTE and an increased CT RV/LV diameter ratio are predictors of PE-related 30-day mortality with similar prognostic significance."


Increased RV/LV Ratio Is An Independent Predictor of PE-Related Mortality

Conclusion:

"...RVD assessed by CT showed an association with an increased risk of mortality in patients with hemodynamically stable PE..."


CTA-Derived RV/LV Ratio Is Reproducible and Reliable

Methodology:

The RV/LV ratio was measured in three-dimensional (3D) reformatted reconstructions, adjusting the axial, coronal, and sagittal planes to view the largest diameter of each ventricle as measured perpendicular to the interventricular septum.

Conclusion:

"The reliability of CTA for PE was excellent for the axial and multiplanar reformatted methods for quantifying the right-to-left ventricular ratio..."

Ouriel et al. Vascular Online First, published on April 18, 2016 as doi:10.1177/1708538116645056
FlowTriever Device ("FT")

- Navigates through the right heart and delivers FT device to the pulmonary artery
- Large bore catheter maximizes aspiration and collection of thrombus

Aspiration Guide Catheter ("AGC")

- Deployed out of AGC and into thrombus
- Disrupts, engages and maximizes volumes of thrombus

Retraction Aspirator ("RA")

- Retracts the FT with disruption of the AGC
- Synchronizes aspiration and retrieval

Disruption, maceration and retrieval of clot

Rapid flow restoration ▶ Reduced PA pressure ▶ Reduced RV strain

FLARE Study Overview

- Objective
  - Evaluate the safety and effectiveness of the FlowTriever System for use in the removal of emboli from the pulmonary arteries in the treatment of acute PE

- Study Design
  - Prospective, single-arm, multicenter study
  - 106 patients, 18 sites
  - Follow-up at 48 hours & 30 days
  - Primary endpoints
    - Effectiveness – reduction in RV/LV ratio at 48-hours
    - Safety – Composite major adverse event rate

Major Adverse Event Definition

- Device-related death
- Major bleeding (VARC-2 definition)
- Treatment-related adverse events:
  - Clinical Deterioration
  - Pulmonary vascular injury
  - Cardiac injury
- All endpoints are measured within 48 hrs ± 8 hours

Study Flow

FLARE was an Investigational Device Exemption ("IDE") study with all appropriate controls including:

- Data Safety and Monitoring Board
- Clinical Events Committee
- Independent Core Lab adjudication of RV/LV ratio for primary effectiveness endpoint
- (Syntactx, LLC, New York, NY, USA)

Patient Selection

Main Inclusion Criteria:

- Age ≥ 18 and ≤ 75 years
- CTA evidence of proximal PE
- PE symptom duration ≤ 14 days
- RV/LV ratio of > 0.9
- Systolic BP ≥ 90 mmHg
- Stable heart rate ≤ 130 bpm

Main Exclusion Criteria:

- Thrombolytic use within 30 days
- HTN with peak PA pressure > 70 mmHg
- Vasopressor requirement after fluids to keep pressure ≥ 90 mmHg
- FIO2 requirement > 40% room air or > 6 LPM to keep O2 sat > 90%
- Hematocrit < 28%, platelets < 100,000/μL, serum creatinine > 1.8 mg/dL, INR > 3
- Cardiovascular or pulmonary surgery within 7 days
- Active/ progressing cancer
- Pregnancy
- Note: No specific exclusion for increased bleeding risk
Baseline Characteristics

- Sites: 18
- Patients treated: 106
- Mean age ± SD, years: 55.6 ± 13.6
- Male gender, n (%): 58 (54.7)
- Caucasian: 87 (82.1)
- Hispanic: 1 (0.9)

Comorbidities

- Hypertension: 60 (56.6)
- Coronary Artery Disease: 10 (9.4)
- Congestive Heart Failure: 6 (5.7)
- PFO / Other Shunt: 4 (3.8)
- COPD: 8 (7.5)
- Chronic Renal Insufficiency: 9 (8.5)
- Concurrent DVT: 73 (68.9)
- Prior Stroke / TIA: 10 (9.4)
- Prior DVT: 14 (13.2)
- Prior PE: 10 (9.4)
- Recent Surgery – Ortho (4), CV (1), Urologic (1): 6 (5.7)

sPESI

- 0: 59/106 (55.7)
- 1: 47/106 (44.3)
- Elevated Cardiac Troponin: 60/101 (59.4)
- Elevated D-Dimer: 45/60 (75.0)
- Elevated B-Natriuretic Peptide: 65/89 (73.0)

PE Location

- Unilateral: 52/106 (4.7)
- Central: 58/106 (4.7)
- Bilateral: 54/106 (50.9)
- Bilateral + Central: 42/106 (39.6)

PE Characteristics

Procedural Characteristics

- Pre-procedure anticoagulation, n (%)
  - UFH: 88 (83.0)
  - LMWH: 22 (20.8)
  - Other – VKA (1), NOAC (5): 6 (5.7)

- Right femoral access, n (%): 101 (95.3)
- Received lytics during procedure, n (%): 2 (1.9)
- Mean # devices used: 1.7
- Mean passes: 3.9 ± 1.7
- Mean procedure time (min): 1 hr 59 mins
- Technical complications (delivery, deployment OR retraction): 0

Subject Disposition

- 106 ITT Subjects Enrolled & Treated
- 106 ITT Subjects Met Eligibility
- 2 Subjects with Post-Ct Not Done
- 2 Subjects with Unreadable Cts
- 2 Subjects Lost to Follow-up
- 104 ITT Subjects Treated Technical 1.7

*Subjects who did not meet eligibility requirements did during follow-up period.
FlowTriever Clot Retrieval Experience, Acute to Chronic

RV/LV Ratio Outcomes

RV/LV Ratio Outcomes

Clinical Outcomes

<table>
<thead>
<tr>
<th>ICU stay post-procedure, median</th>
<th>3 day</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU stay: distribution</td>
<td>0 = 44</td>
</tr>
<tr>
<td></td>
<td>1 = 23</td>
</tr>
<tr>
<td></td>
<td>2 = 18</td>
</tr>
<tr>
<td></td>
<td>3+ = 22</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Days to discharge post-procedure, median</th>
<th>3 days</th>
</tr>
</thead>
<tbody>
<tr>
<td># Patients lost to follow-up</td>
<td>2</td>
</tr>
<tr>
<td># Patients any-cause mortality</td>
<td>1</td>
</tr>
<tr>
<td># MAEs*</td>
<td>4 (ITT 3.8%, mITT 3.8%)</td>
</tr>
</tbody>
</table>

Major Adverse Events

- No intracranial hemorrhage
- No access-site major bleeding
- No device-related death
- No device-related pulmonary injury
- No device-related cardiac injury
- One patient had a bleeding event
- Three patients had treatment-related clinical deterioration
Major Adverse Events

<table>
<thead>
<tr>
<th>MAE Subject #</th>
<th>MAE Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>#0404</td>
<td>Hemoptysis, hemothorax, pulmonary infarction; lower lobectomy; possible reperfusion injury</td>
</tr>
<tr>
<td>#0808</td>
<td>Worsening PE, surgical embolectomy</td>
</tr>
<tr>
<td>#2101</td>
<td>Cardiogenic shock, acute respiratory insufficiency</td>
</tr>
<tr>
<td>#2422</td>
<td>Patient agitated during procedure despite sedation; respiratory arrest with VSD and cardioversion</td>
</tr>
</tbody>
</table>

FLARE Effectiveness in Context

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>N</th>
<th>Efficacy at RV/LV Ratio of Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLARE</td>
<td>FlowTriever mechanical thrombectomy</td>
<td>26</td>
<td>-</td>
</tr>
<tr>
<td>HALLETTE II (2012)</td>
<td>UGART</td>
<td>20</td>
<td>0.39 / 25%</td>
</tr>
<tr>
<td>FLARE</td>
<td>FlowTriever mechanical thrombectomy</td>
<td>26</td>
<td>0.39 / 25%</td>
</tr>
<tr>
<td>ULTIMA (USAT arm)</td>
<td>UGART</td>
<td>30</td>
<td>0.42 / 24%</td>
</tr>
<tr>
<td>PEITHO (tPA arm)</td>
<td>UGART</td>
<td>30</td>
<td>0.31 / 24%</td>
</tr>
<tr>
<td>SEATTLE II</td>
<td>Systemic Thrombolysis</td>
<td>15</td>
<td>0.29 / 22%</td>
</tr>
<tr>
<td>B flowTriever</td>
<td>Systemic Thrombolysis</td>
<td>17</td>
<td>0.31 / 24%</td>
</tr>
<tr>
<td>Fasullo et al (2011)</td>
<td>Systemic Thrombolysis</td>
<td>35</td>
<td>0.40 / 27%</td>
</tr>
<tr>
<td>Mi et al (2013)</td>
<td>Systemic Thrombolysis</td>
<td>57</td>
<td>0.11 / 8%</td>
</tr>
</tbody>
</table>

FLARE Safety in Context

<table>
<thead>
<tr>
<th>Study</th>
<th>Major Bleeding</th>
<th>Intracranial Hemorrhage (Within/Group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLARE</td>
<td>1(0.4%)</td>
<td>1(0.4%)</td>
</tr>
<tr>
<td>ULTIMA (USAT arm)</td>
<td>0(0.0%)</td>
<td>0(0.0%)</td>
</tr>
<tr>
<td>PEITHO (tPA arm)</td>
<td>0(0.0%)</td>
<td>0(0.0%)</td>
</tr>
<tr>
<td>SEATTLE II</td>
<td>1(0.4%)</td>
<td>1(0.4%)</td>
</tr>
</tbody>
</table>

**Conclusions**

- Catheter-directed mechanical thrombectomy using the FlowTriever System, without the use of thrombolytics, is safe and effective in improving RV function in patients with intermediate-risk PE.
- Additionally, it has the potential to reduce bleeding complications and reduce total hospital and ICU length of stay.
- This study establishes mechanical thrombectomy for acute pulmonary embolism as a viable alternative to thrombolytic-based catheter-directed therapy and warrants further investigation.

FLARE Investigators

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- Adam Tu, M.D.

11/13/2018

Cases
First patient experience

- 43 year old woman with mild obesity
- Otherwise healthy and moderately active
- Presents with 2 week of progressive dyspnea and left leg pain/swelling
- Syncope after climbing up 1 flight of stairs
- Father had DVT/PE history

Clinical History

- BP 132/97, HR 92, O2 sat 96% on 1 L NC
- HCT 33.6, Hb 11.4, Plt 217
- TnT <0.03, pro-BNP 1649 (5-450)
- D-Dimer 2.12 (0-0.49)
- BUN 9, Cr 0.76
- Ultrasound L leg: 1 femoral DVT
- CTA (PE protocol): bilateral PE
Procedure Details
- Case time 2 hours 30 minutes
- Number of aspirations: 7
- Contrast usage 340 cc
- Fluoroscopy time 35 minutes
- Air KERMA 0.3 Gy

Follow up
- Initial: RA 18/16/33, RV 54/14, PA 54/23/34
- Post: RA 11/10/6, RV 41/6, PA 42/17/28, PCWP 22/19/18
- Patient was observed in the post-PCI unit overnight
- Transitioned to oral apixaban the following day
- Discharged on post-procedure day 2
- No complaints on 1 month follow-up
- Normal RV size and function at 3 month echo

48 hour CTA

Mid-experience (~50 patients later)
- 47 year old woman with recent ankle fracture and leg immobilization
- 3 days of leg swelling and dyspnea with near-syncope
- CTA shows saddle pulmonary embolus with RV/LV ratio of 1.5:1
- HR 110
- BNP and troponin mildly positive
Procedural Details

- Total case time: 49 minutes
- Number of aspirations: 2
- Contrast usage: 80 cc
- Fluoroscopy: 7.4 minutes
- Air KERMA: 0.1 Gy

- Pre-procedure PA 5/2/18
- Post-procedure PA 28/5/18

Clinical Course

- The patient reports immediate improvement in dyspnea
- No ICU stay. Observed in post-PCI unit overnight
- Changed to oral apixaban in am and discharged the next day.
Protocol Deviations

<table>
<thead>
<tr>
<th>Type of Deviation</th>
<th># of Events</th>
<th># (%) of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>40</td>
<td>35 (33.0%)</td>
</tr>
<tr>
<td>Ineligible subject enrolled</td>
<td>1</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>Informed consent not obtained/sign/dated</td>
<td>0</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Missing Assessment Prescribed by Protocol</td>
<td>3</td>
<td>3 (3.0%)</td>
</tr>
<tr>
<td>Assessment Performed Outside Protocol Window</td>
<td>7</td>
<td>7 (6.6%)</td>
</tr>
<tr>
<td>Visit Performed Outside Protocol Window</td>
<td>29</td>
<td>27 (25.5%)</td>
</tr>
</tbody>
</table>

Limitations

- The single-arm study design precluded direct comparison with the efficacy and safety of systemic fibrinolysis or anticoagulation alone.
- Our study design did not allow for evaluation of clinical end points such as hemodynamic collapse or mortality.

Poolability – RV/LV Analysis

<table>
<thead>
<tr>
<th>Analysis</th>
<th>N</th>
<th>Mean (SE)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANOVA of Change in RV/LV Ratio from Baseline to 48-hour</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>5</td>
<td>0.44 (0.09)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>6</td>
<td>0.27 (0.05)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>5</td>
<td>0.33 (0.08)</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>3</td>
<td>0.53 (0.30)</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>16</td>
<td>0.34 (0.09)</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>7</td>
<td>0.43 (0.16)</td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>9</td>
<td>0.19 (0.10)</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>9</td>
<td>0.30 (0.08)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>8</td>
<td>0.41 (0.08)</td>
<td></td>
</tr>
<tr>
<td>J</td>
<td>10</td>
<td>0.39 (0.05)</td>
<td></td>
</tr>
</tbody>
</table>

FLARE vs. SEATTLE II

<table>
<thead>
<tr>
<th>FLARE</th>
<th>SEATTLE II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients / Sites</td>
<td>106 patients / 18 sites</td>
</tr>
<tr>
<td>Safety Endpoints</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Composite MAE at 48-Hours = 3.8% (n=4)</td>
</tr>
<tr>
<td>2</td>
<td>30-Day Mortality = 0.9% (n=1)</td>
</tr>
<tr>
<td>Primary Efficacy Endpoint</td>
<td>Reduction in RV/LV ratio at 48 hours: 0.39 / 25% (n=106; OPC = &gt;0.12)</td>
</tr>
<tr>
<td>ICU Stay</td>
<td>Median = 1 day</td>
</tr>
<tr>
<td>Percentage with ICU stay</td>
<td>58% (n=62)</td>
</tr>
<tr>
<td>Length of Hospital Stay</td>
<td>Mean = 4.1 days</td>
</tr>
</tbody>
</table>

Device Metrics

- Mean # FT devices/case = 1.7
- Mean # passes/case = 3.9
- Mean total dose tPA = 24 mg