Insights on Selected Procoagulation markers and Outcomes in Stroke Trial (iSPOT) Primary results

Financial Disclosures

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  - NINDS 1U01NS079077 (iSPOT)
  - NINDS 1U01NS069498 (SHINE)

• No Unlabelled/Unapproved disclosure
Background

- Acute stroke with hyperglycemia is associated with worse functional outcomes

- Tissue factor pathway markers of blood coagulation are elevated in acute ischemic stroke

- These markers are considerably higher in patients with hyperglycemia

- Need for a study of the effects of blood glucose control on blood coagulation markers and their relationship to stroke outcomes.
Design and Intervention

• Subset of patients enrolled in the SHINE trial
• SHINE treatment arms:
  ❖ Intensive control - target blood glucose 80-130 mg/dL
  ❖ Standard treatment - target blood glucose <180 mg/dL
• SHINE functional outcome – NIHSS adjusted mRS at 90 days
• Compare markers of blood coagulation by treatment, by functional outcome, and the interaction between treatment and outcome
Main iSPOT Eligibility Criteria

• SHINE Eligible
  - AIS <12 hours from onset
  - NIHSS 3-22
  - BG > 110 mg/dL if history of diabetes or BG ≥150 mg/dL if no history of diabetes

• Exclusions
  - Systemic anticoagulation
  - Known hepatic insufficiency (INR>1.5 or hx variceal bleeding or hepatic encephalopathy)
  - History of thrombotic or hypercoagulable condition
**Tissue Factor Pathway of Blood Coagulation**

**iSPOT measurements**

- Tissue Factor Pathway Inhibitor (TFPI)
- Tissue Factor (TF-PCA)
  - FVII
  - FX
  - FXa
  - FVIII

- Antithrombin
- Prothrombin
- Va
- Thrombin
- Fibrinogen
- Fibrin
- Plasminogen
- Plasmin

- Crosslinked Fibrin
- Fibrin Degradation Products (D-Dimer)

- PAI-1
- t-PA

**Activation**
**Inhibition**
**Inactivation, degradation**
Enrollment by Site

Subjects Enrolled

Hub/Ancillary site

- NYP: 40
- Emory: 35
- Ohio State: 27
- Kentucky: 21
- Augusta: 18
- Temple: 16
- Cincinnati: 12
- UTSW: 9
- Texas: 9
- Pittsburgh: 8
- Mayo Florida: 8
- Wayne: 7
- UVA: 7
- Stanford: 7
- WVU: 6
- Iowa: 6
- Wisconsin: 6
- Minnesota: 6
- UPenn: 3
- UCLA: 3
- HFHS: 3
- Buffalo: 3
- Arizona: 3
- Utah: 2
- SUNY Downstate: 2
- Mt. Sinai: 2
- St. Thomas: 1
- Medstar: 1
- Maryland: 1
- UCSF: 0
- OSF St Francis: 0
- Mass General: 0
- Jackson Memorial Hospital: 0
- Cornell: 0

Enrollment Total = 270
NETT = 208
Ancillary = 62
## Characteristics of the Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intensive (N=135)</th>
<th>Standard (N=135)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHINE functional outcome</td>
<td>Favorable (N=30)</td>
<td>Favorable (N=20)</td>
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<tr>
<td></td>
<td>Unfavorable (N=102)</td>
<td>Unfavorable (N=112)</td>
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<tr>
<td>Age (yr)-median (IQR)</td>
<td>67 (58-71)</td>
<td>63.5 (57-71)</td>
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<td>64.5 (55-74)</td>
<td>66 (56-73)</td>
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<tr>
<td>Female sex–no. (%)</td>
<td>9 (30.0)</td>
<td>8 (40.0)</td>
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<td>42 (41.2)</td>
<td>47 (42.0)</td>
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<td>Previous hx of Diabetes mellitus-no. (%)</td>
<td>23 (76.7)</td>
<td>16 (80.0)</td>
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<td></td>
<td>83 (81.4)</td>
<td>92 (82.1)</td>
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<tr>
<td>Blood glucose levels (mg/dL, mean (IQR)</td>
<td>167 (148-208)</td>
<td>177 (144-215)</td>
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<tr>
<td>Initial</td>
<td>163 (120-232)</td>
<td>184 (145-237)</td>
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<tr>
<td>48-Hr</td>
<td>98 (91-138)</td>
<td>150 (110-175)</td>
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<tr>
<td></td>
<td>106.5 (94-134)</td>
<td>187 (144-235)</td>
</tr>
<tr>
<td>IV tPA treated - no. (%)</td>
<td>15 (50.0)</td>
<td>9 (45.0)</td>
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<tr>
<td></td>
<td>49 (48.0)</td>
<td>43 (38.4)</td>
</tr>
<tr>
<td>NIHSS at randomization–median (IQR)</td>
<td>7 (3-11)</td>
<td>7 (4-10.5)</td>
</tr>
<tr>
<td></td>
<td>7 (4-12)</td>
<td>7 (5-11)</td>
</tr>
<tr>
<td>Stoke onset to baseline (hr)-median (IQR)</td>
<td>8.3 (6-9.7)</td>
<td>9.4 (7.3-11.1)</td>
</tr>
<tr>
<td></td>
<td>9.0 (7.4-11.5)</td>
<td>9.1 (7.0-11.3)</td>
</tr>
</tbody>
</table>
P values represent comparisons between baseline and 48-hr levels for each marker by tPA treatment. Value is adjusted using Tukey’s method for multiple comparisons. **p < 0.05, ***p < 0.01
P values represent comparisons between Intensive and Standard groups in terms of changes from baseline to 48 hours by tPA treatment regardless functional outcome. **p < 0.05
Change in factor levels by SHINE treatment group

P values represent comparisons between Intensive and Standard groups in terms of changes from baseline to 48 hours by tPA treatment regardless functional outcome. **p < 0.05
Change in factor levels by functional outcome

P values represent comparisons between Favorable and Unfavorable groups in terms of changes from baseline to 48 hours by tPA treatment regardless of treatment group. * p < 0.1, ***p < 0.01
Relationship of change in factor levels and functional outcome: intensive BG control

P values represent comparisons between Favorable and Unfavorable groups in terms of changes from baseline to 48 hours by tPA treatment in intensive group. ** p < 0.05, ***p < 0.01
P values represent comparisons between Favorable and Unfavorable groups in terms of changes from baseline to 48 hours by tPA treatment in standard group. ***p < 0.01
Summary and significance

Tissue Factor (TF-PCA)

Tissue Factor Pathway Inhibitor (TFPI)

Tissue Factor (TF)

FVII

FX

FVIIa

FVIII

FXa

FXa

Prothrombin

Va

Thrombin

Antithrombin

Antithrombin (TAT)

Fibrinogen

Fibrin

Plasminogen

Plasmin

Fibrin Degradation Products (D-Dimer)

PAI-1

t-PA

FXIIIa

FXIII

Crosslinked Fibrin

Activation

Inhibition

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The SHINE-iSPOT Team!