Imaging-Based Acute Stroke Studies: DIAS-2, TNK, DEFUSE 2, MR RESCUE

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Georgetown University
Imaging Biomarkers in Acute Stroke Trial Design

Key Clinical Inclusion Criteria

Randomization

Treatment

Control

Outcomes

Clinical Outcomes

- Day 90 mRS
Imaging Biomarkers in Acute Stroke Trial Design

- Surrogate or auxiliary biomarkers or endpoints
  - Correspond to clinical outcome to test response (harm or benefit) to an intervention with potentially smaller sample size

Key Clinical Inclusion Criteria

Randomization

Treatment  Control

Outcomes

Clinical Outcomes
- Day 90 mRS

Imaging Outcomes
- Infarct volume or infarct growth
- Revascularization
- Hemorrhagic Transformation
Imaging Biomarkers in Acute Stroke Trial Design

- **Prediction (selection) biomarkers**
  - Predict response to therapy by including only target disease state and/or excluding those unlikely to benefit or likely to be harmed

- **Key Clinical Inclusion Criteria**

- **Imaging Selection Criteria**
  - Penumbral Imaging
  - Target Vessel Imaging

- **Randomization**
  - Treatment
  - Control

- **Outcomes**
  - **Clinical Outcomes**
    - Day 90 mRS
  - **Imaging Outcomes**
    - Infarct volume or infarct growth
    - Revascularization
    - Hemorrhagic Transformation
Ideal Imaging Selection Biomarker Development

- Identifying Biomarker: RCT including all potential subjects followed by a responder analysis
- Validating Biomarker: RCT to demonstrate those with (or without biomarker) are in fact the sole responders
- Applying Biomarker to Test Putative Therapies: Enroll only subjects with target prediction imaging marker
  - If selection biomarker is not valid or optimized,
    - Patients who may actually benefit from therapy may be inadvertently excluded, and/or
    - It may be concluded that biomarker selection is beneficial when in fact only a treatment effect is being detected
Validating the Penumbral Imaging Selection Hypothesis: Trial Design

Acute Stroke

Multimodal Imaging

Randomization (Stratified by Penumbral Pattern)

Penumbral Pattern
  - Active Tx
  - Control

Non-Penumbral Pattern
  - Active Tx
  - Control
Validating the Penumbral Imaging Selection Hypothesis: Trial Design

- Acute Stroke
  - Multimodal Penumbral Imaging
    - Randomization (Stratified by Penumbral Pattern)
      - Penumbral Pattern
        - Active Tx + Response
        - Control - Response
      - Non-Penumbral Pattern
        - Active Tx - Response
        - Control - Response
Validating the Penumbral Imaging Selection Hypothesis: Trial Design - MR RESCUE

- Acute Stroke
  - Multimodal Penumbral Imaging
    - Randomization (Stratified by Penumbral Pattern)
      - Penumbral Pattern
        - Active Tx + Response
        - Control - Response
      - Non-Penumbral Pattern
        - Active Tx - Response
        - Control - Response
Validating the Penumbral Imaging Selection Hypothesis: Trial Design - DEFUSE 2

Acute Stroke

Multimodal Penumbral Imaging

Randomization (Stratified by Penumbral Pattern)

Penumbral Pattern
  - Active Tx
  - + Response

Non-Penumbral Pattern
  - Active Tx
  - - Response
Applying Biomarker to Test Putative Therapies: Trial Design

Acute Stroke

Multimodal Imaging

Penumbral Pattern

Active Tx 1

Control or Active Tx 2

Non-Penumbral Pattern: Excluded
Applying Biomarker to Test Putative Therapies: Trial Design

Acute Stroke

Multimodal Imaging

Penumbral Pattern

Active Tx 1
+ Response

Control or Active Tx 2
- Response

Non-Penumbral Pattern: Excluded
Applying Biomarker to Test Putative Therapies: Trial Design - DIAS 2, TNK

Acute Stroke

Multimodal Imaging

Penumbral Pattern

Active Tx 1
+ Response

Control or Active Tx 2
- Response

Non-Penumbral Pattern: Excluded
Comparing and contrasting how imaging selection and outcome markers have been applied in trials to date: DIAS-2, TNK, DEFUSE 2, MR RESCUE

Key Clinical Inclusion Criteria

Imaging Selection Criteria
- Penumbral Imaging
- Target Vessel Imaging

Randomization

Treatment

Control

Outcomes

Clinical Outcomes
- Day 90 mRS

Imaging Outcomes
- Infarct volume or infarct growth
- Revascularization
- Hemorrhagic Transformation
Intravenous desmoteplase in patients with acute ischaemic stroke selected by MRI perfusion–diffusion weighted imaging or perfusion CT (DIAS-2): a prospective, randomised, double-blind, placebo-controlled study


Lancet Neurol 2009; 8: 141–50
Published Online
December 18, 2008
DOI:10.1016/S1474-4422(08)70267-9
DIAS-2
Phase III Randomized, placebo-controlled, dose-ranging study

Key Clinical Inclusion Criteria
- 3-9 hrs
- NIHSS 4-24

Key Imaging Inclusion Criteria
- ≥ 20% estimated CT or MRI mismatch

Randomization

IV Desmoteplase

90 μg/kg n=57
125 μg/kg n=66
Placebo n=63

Outcomes

Clinical Outcomes
- D90 good outcome: NIHSS improvement ≥ 8 and mRS 0-2 and BI 75-100

Imaging Outcomes
- D30 lesion growth
DIAS-2 Cohort Characteristics

• Clinical
  ➢ Mean Age 71-73.5
  ➢ Median NIHSS 9
  ➢ Median Time to Tx 6.4-6.6 Hrs

• Imaging
  ➢ Median Infarct Core - MRI/CT 6.8-11.7 / 10.9-17.1
  ➢ Median Perfusion Lesion 52.5 ml
  ➢ Target Vessel Occlusion NA
  ➢ Screened with MRI 66%
DIAS-2: Key Results

Primary Outcome Responder Rates

- Desmoteplase 90 μg/kg: 47%
- Placebo: 36%
- Hacke, Lancet Neurology 2009
DIAS-2: Key Results

Primary Outcome Responder Rates

- Desmoteplase 90 μg/kg: 47%
- Placebo: 36%
- p=0.47

Differences in CT vs. MRI characteristics raised the concern that the two modalities differed in penumbral prediction

-Hacke, Lancet Neurology 2009
Pooled Desmoteplase Analyses

Percent Good Clinical Response
OR: 2.83

MRI patients with MMV > 60 mL

Warach et al, Stroke 2012

Patients with baseline vessel imaging TIMI 0-1

Fiebach et al, Stroke 2012
A Randomized Trial of Tenecteplase versus Alteplase for Acute Ischemic Stroke

Mark Parsons, M.D., Neil Spratt, M.D., Andrew Bivard, B.Sc., Bruce Campbell, M.D., Kong Chung, M.D., Ferdinand Miteff, M.D., Bill O’Brien, M.D., Christopher Bladin, M.D., Patrick McElduff, Ph.D., Chris Allen, M.D., Grant Bateman, M.D., Geoffrey Donnan, M.D., Stephen Davis, M.D., and Christopher Levi, M.D.
TNK
Phase IIb, prospective, randomized, open-label blinded endpoint trial

Key Clinical Inclusion Criteria
• ≤ 6 hrs
• NIHSS > 4
• Standard IV tPA criteria

Key Imaging Inclusion Criteria
• CTA: MCA, ACA, PCA Occlusion
• PCT Core < 1/3 MCA, ½ PCA/ACA
• > 20% mismatch, PCT > 20 mL

Randomization

IV Tenecteplase

0.1 mg/kg
n=25

0.25 mg/kg
n=25

IV Alteplase 0.9 mg/kg
n=25

Outcomes

Clinical Outcomes
• 24 Hr Change in NIHSS from baseline
• D90 mRS

Imaging Outcomes
• 24 Hr mean % reperfusion
• D90 infarct growth
TNK Cohort Characteristics

- Clinical
  - Mean Age: 70
  - Mean NIHSS: 14.4
  - Time to Tx: 2.7 - 3.1 Hrs

- Imaging
  - Median Infarct Core: 8-13 mL
  - Median Perfusion Lesion: 76-80 mL
  - Target Vessel Occlusion: 96% (theoretically 100%)

Parsons et al NEJM 2012
TNK Key Results

Mean Reperfusion at 24 Hrs (%)

- tPA: 50
- TNK: 79.3

Mean 24 Hr Improvement in NIHSS

- tPA: 3
- TNK: 8

Parsons et al NEJM 2012
TNK Dose-Tier Analysis

Reperfusion at 24 Hrs

Change in NIHSS at 24 Hrs

Parsons et al NEJM 2012
TNK: Day 90 mRS 0-2

- tPA
- TNK 0.1 mg/kg: 60%
- TNK 0.25 mg/kg: 84%
MRI profile and response to endovascular reperfusion after stroke (DEFUSE 2): a prospective cohort study

Maarten G Lansberg, Matus Straka, Stephanie Kemp, Michael Mlynash, Lawrence R Wechsler, Tudor G Jovin, Michael J Wilder, Helmi L Lutsep, Todd J Czartoski, Richard A Bernstein, Cherylee W J Chang, Steven Warach, Franz Fazekas, Manabu Inoue, Aaryani Tipirneni, Scott A Hamilton, Greg Zaharchuk, Michael P Marks, Roland Bammer, Gregory W Albers, for the DEFUSE 2 study investigators*

Published Online
September 4, 2012
http://dx.doi.org/10.1016/S1474-4422(12)70203-X
DEFUSE 2
Multicenter prospective cohort study

**Key Clinical Inclusion Criteria**
- ≤ 12 hrs
- NIHSS ≥ 5
- IV tPA pts eligible

**Key Imaging Inclusion Criteria**
- Baseline MRI with DWI/PWI

**Endovascular Candidates**

**Target Mismatch**
- n=78

**No Target Mismatch**
- n=26

*Criteria: Tmax > 6s / thresholded ADC < 600 > 1.8 and Thresholded ADC (DWI) < 70 cc and Tmax > 10 s < 100 cc

**Outcomes**

**Clinical Outcomes**
- D30 NIHSS improvement ≥ 8 or D30 NIHSS 0-1
- D90 mRS (secondary)

**Imaging Outcomes**
- Post-procedural TICI on angiography
- 12 hrs post procedure scan > 50% reperfusion
- D5 FLAIR infarct growth
DEFUSE 2 Cohort Characteristics

• Clinical
  - Mean Age 66
  - Mean NIHSS 16
  - Median Time to Tx 5.9 Hrs

• Imaging
  - Median Infarct Core (DWI Volume) 15 mL
  - Median Perfusion Lesion 79 mL
  - Target Vessel Occlusion NA

• Outcomes
  - TICI 2b-3 Rate (angiography) 46%

Lansberg et al Lancet Neurology 2012
DEFUSE 2 Key Results

Primary Analysis: Comparison of the odds ratios for the association between reperfusion and FCR: Target Mismatch vs. No Target Mismatch

<table>
<thead>
<tr>
<th>Odds Ratios</th>
<th>No Target Mismatch (n=21)</th>
<th>Target Mismatch (n=78)</th>
<th>p for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>0.2 (0.0 – 1.4)</td>
<td>5.0 (1.9 – 13)</td>
<td>0.004</td>
</tr>
<tr>
<td>Adjusted for Age and DWI</td>
<td>0.2 (0.0 – 1.6)</td>
<td>8.8 (2.7 – 29)</td>
<td>0.003</td>
</tr>
</tbody>
</table>
DEFUSE 2 Key Results

<table>
<thead>
<tr>
<th>Target Mismatch</th>
<th>Reperfusion N=46</th>
<th>No Reperfusion N=32</th>
</tr>
</thead>
<tbody>
<tr>
<td>90-days mRS score</td>
<td>0 to 2 57%</td>
<td>3 to 4 28%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0 to 2 31%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No Target Mismatch</th>
<th>Reperfusion N=12</th>
<th>No Reperfusion N=9</th>
</tr>
</thead>
<tbody>
<tr>
<td>90-days mRS score</td>
<td>0 to 2 25%</td>
<td>3 to 4 42%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0 to 2 22%</td>
</tr>
</tbody>
</table>

Slide provided by Greg Albers
A Trial of Imaging Selection and Endovascular Treatment for Ischemic Stroke

Chelsea S. Kidwell, M.D., Reza Jahan, M.D., Jeffrey Gornbein, Dr.P.H., Jefry R. Alger, Ph.D., Val Nenov, Ph.D., Zahra Ajani, M.D., Lei Feng, M.D., Ph.D., Brett C. Meyer, M.D., Scott Olson, M.D., Lee H. Schwamm, M.D., Albert J. Yoo, M.D., Randolph S. Marshall, M.D., Philip M. Meyers, M.D., Dileep R. Yavagal, M.D., Max Wintermark, M.D., Judy Guzy, R.N., Sidney Starkman, M.D., and Jeffrey L. Saver, M.D., for the MR RESCUE Investigators*
MR RESCUE
Phase II b, multicenter, randomized, controlled, blinded outcome trial

Key Clinical Inclusion Criteria
- ≤ 8 hrs
- NIHSS 6-29

Key Imaging Inclusion Criteria
- MRA/CTA: ICA/MCA Occlusion

Randomization

Favorable Penumbral Pattern
- Standard Care n=34
- Embolectomy* n=34

Non-Penumbral Pattern
- Standard Care n=20
- Embolectomy* n=30

Outcomes

Clinical Outcomes
- D90 modified Rankin Scale

Imaging Outcomes
- D7 MRA/CTA Revascularization
- D7 PWI/PCT Reperfusion
- D7 Infarct Volume and Lesion Growth

*with Merci Retriever or Penumbra System
Multimodal MRI Examples

Favorable = predicted infarct core ≤ 90 cc & ratio of predicted infarct tissue within at-risk region ≤ 70% (voxel-based multivariate MRI and CT models)
MR RESCUE Cohort Characteristics

127 subjects were enrolled between 2004-2011; of these, 118 were fully eligible

- Clinical
  - Mean Age 65.5
  - Median NIHSS 17
  - Median Time to Enrollment 5.5 Hrs
  - Median Time to Treatment* 6.3 Hrs

- Imaging
  - Median Infarct Core 60.2 mL†
  - Median Perfusion Lesion 177.6 mL
  - Target Vessel Occlusion 100%

- Outcomes
  - TICI 2a-3 (2b-3) Rate (angiography*) 67% (27%)
  - sICH Rate 4%

†Larger for CT vs. MRI, *Embolectomy arm only
Primary Outcome Analyses

Primary Hypothesis: Test for Interaction between treatment assignment and penumbral pattern by shift analysis

<table>
<thead>
<tr>
<th></th>
<th>E/Pen n=34</th>
<th>S/Pen n=34</th>
<th>E/Non-Pen n=30</th>
<th>S/Non-Pen n=20</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (95% CI) Day 90 mRS</td>
<td>3.9 (3.3-4.4)</td>
<td>3.4 (2.8-4.0)</td>
<td>4.0 (3.4-4.6)</td>
<td>4.4 (3.6-5.2)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

As such, the trial failed to demonstrate that penumbral imaging identified patients who would differentially benefit from endovascular therapy for acute ischemic stroke
## Primary Outcome Analyses

### Nested Hypothesis 1: Test for treatment efficacy in Penumbral Patients

<table>
<thead>
<tr>
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<th>E/Pen n=34</th>
<th>S/Pen n=34</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (95% CI) Day 90 mRS</td>
<td>3.9 (3.3-4.4)</td>
<td>3.4 (2.8-4.0)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

### Nested Hypothesis 2: Test for absence of treatment efficacy (equivalency) in Non-Penumbral Patients

<table>
<thead>
<tr>
<th></th>
<th>E/Non-Pen n=30</th>
<th>S/Non-Pen n=20</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (95% CI) Day 90 mRS</td>
<td>4.0 (3.4-4.6)</td>
<td>4.4 (3.6-5.2)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

### Nested Hypothesis 3: Test for treatment efficacy in Embolectomy vs. Standard Care Patients

<table>
<thead>
<tr>
<th></th>
<th>Embolectomy n=64</th>
<th>Standard Care n=54</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (95% CI) Day 90 mRS</td>
<td>3.9 (3.5-4.3)</td>
<td>3.9 (3.4-4.4)</td>
<td>0.99</td>
</tr>
</tbody>
</table>
Primary Analyses: Age Adjusted

Primary Hypothesis: Test for Interaction between treatment assignment and penumbral pattern by shift analysis

<table>
<thead>
<tr>
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<th>E/Pen n=34</th>
<th>S/Pen n=34</th>
<th>E/Non-Pen n=30</th>
<th>S/Non-Pen n=20</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (95% CI) Day 90 mRS</td>
<td>3.8 (3.2-4.4)</td>
<td>3.4 (2.9-3.9)</td>
<td>4.3 (3.8-4.7)</td>
<td>4.2 (3.7-4.8)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Nested Hypothesis 1: Test for treatment efficacy in Penumbral Patients

<table>
<thead>
<tr>
<th></th>
<th>E/Pen n=34</th>
<th>S/Pen n=34</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (95% CI) Day 90 mRS</td>
<td>3.8 (3.2-4.4)</td>
<td>3.4 (2.9-3.9)</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Nested Hypothesis 2: Test for absence of treatment efficacy (equivalency) in Non-Penumbral Patients

<table>
<thead>
<tr>
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<th>S/Non-Pen n=20</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (95% CI) Day 90 mRS</td>
<td>4.3 (3.8-4.7)</td>
<td>4.2 (3.7-4.8)</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Nested Hypothesis 3: Test for treatment efficacy in Embolectomy vs. Standard Care Patients

<table>
<thead>
<tr>
<th></th>
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<th>Standard Care n=54</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (95% CI) Day 90 mRS</td>
<td>4.0 (3.7-4.4)</td>
<td>3.8 (3.4-4.2)</td>
<td>0.36</td>
</tr>
</tbody>
</table>
Day 90 mRS by Imaging Pattern

Patients (%)

Penumbral: 600% 1200% 600% 1900% 2400% 1500% 1900%

n-Penumbral: 600% 600% 1800% 2200% 2200% 2400% 2400%

p=0.01
Day 90 mRS*

Funded by NINDS/NIH

*Age adjusted
A receiver operator curve exploratory analysis failed to identify a threshold of predicted core volume that would have yielded a significant difference in outcomes based on treatment assignment and favorable penumbral pattern.
## Clinical Outcomes and Infarct Growth

<table>
<thead>
<tr>
<th>Outcome and Measure</th>
<th>Yes</th>
<th>No</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reperfusion (&gt; 90% Tmax volume reduction)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>43</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Mean score on modified Rankin scale (95% CI)</td>
<td>3.2 (2.6-3.8)</td>
<td>4.1 (3.7-4.5)</td>
<td>0.04</td>
</tr>
<tr>
<td>Median absolute infarct growth (inter-quartile range) – mL</td>
<td>9.0 (-13.7-50.3)</td>
<td>72.5 (5.6-120.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Partial or complete revascularization (TICI 2a-3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>79</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Mean score on modified Rankin scale (95% CI)</td>
<td>3.5 (3.1-3.9)</td>
<td>4.4 (4.0-4.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>Median absolute infarct growth (inter-quartile range) – mL</td>
<td>17.7 (-8.8-89.2)</td>
<td>60.3 (19.9-93.3)</td>
<td>0.10</td>
</tr>
</tbody>
</table>
Day 90 mRS By Day 7 Revascularization Status

Had we not included the control arm, we would not have been able to show that the benefit from revascularization at this timepoint was not an acute embolectomy treatment effect!
Trial Limitations

- Long duration for study recruitment (8 years)
- Inclusion of only first generation devices
  - Modest recanalization rates
- Baseline imaging: single snapshot in time
- Relatively late time to enrollment (whole cohort) and time to groin puncture (for the embolectomy arm)
MR RESCUE Conclusion

• MR RESCUE failed to confirm the primary hypothesis of penumbral imaging selection of patients for endovascular therapy for acute ischemic stroke

• MR RESCUE failed to support the hypotheses of
  ➢ Treatment efficacy in favorable penumbral pattern patients
  ➢ Equivalency in non-penumbral pattern patients
  ➢ Efficacy of embolectomy vs. standard care

• Possible reasons for neutral results include
  ➢ Low recanalization rates with 1st generation devices
  ➢ Large predicted infarct cores compared to other studies (including pen group)
  ➢ Introduction of two imaging modalities, which may differ in penumbral prediction
  ➢ Potential for favorable outcomes in penumbral patients regardless of treatment (due to collateral support until spontaneous recanalization)
  ➢ Flawed penumbral imaging selection hypothesis (as currently conceived)
# Trial Design Comparisons

<table>
<thead>
<tr>
<th></th>
<th>DIAS-2 (n=186)</th>
<th>TNK (n=75)</th>
<th>DEFUSE 2 (n=104)</th>
<th>MR RESCUE (N=118)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Imaging Selection</strong></td>
<td>Enrolled only target cases: enhance likelihood of positive outcome</td>
<td>Enrolled all cases: test imaging selection hypothesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Imaging Selection: “Penumbra”</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No†</td>
<td>No</td>
</tr>
<tr>
<td><strong>Penumbral Definition</strong></td>
<td>20% Visual MM</td>
<td>&gt; 20% PCT MM, PCT &gt; 20 mL</td>
<td>Rapid: Target MM</td>
<td>Multivariate Models</td>
</tr>
<tr>
<td><strong>Time Window</strong></td>
<td>3-9</td>
<td>≤ 6 Hrs</td>
<td>&lt; 12 Hrs</td>
<td>&lt; 8 Hrs</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>IV Desmoteplase vs. Placebo</td>
<td>IV TNK vs. IV tPA</td>
<td>Emb.</td>
<td>Emb. vs. SC.</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Phase III, RCT</td>
<td>Phase IIb, PROBE</td>
<td>Prospective, Cohort</td>
<td>Phase IIb, PROBE</td>
</tr>
<tr>
<td><strong>Imaging Modality</strong></td>
<td>MRI and CT</td>
<td>CT</td>
<td>MRI</td>
<td>MRI and CT</td>
</tr>
<tr>
<td><strong>Imaging Selection: Vessel</strong></td>
<td>None</td>
<td>Target Occl.</td>
<td>None</td>
<td>Target Occl.</td>
</tr>
</tbody>
</table>

*Mean, †Sites had option to exclude large cores per standard approach for endovascular therapy*
### Trial Results Comparisons

|                      | DIAS-2  
n=186 | TNK  
n=75 | DEFUSE 2  
n=104 | MR RESCUE  
N=118 |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to Treatment</td>
<td>6.4-6.6 Hrs</td>
<td>2.7-3.1 Hrs</td>
<td>5.9 Hrs</td>
<td>6.3 Hrs</td>
</tr>
<tr>
<td>Median NIHSS</td>
<td>9</td>
<td>14.4*</td>
<td>16*</td>
<td>17</td>
</tr>
<tr>
<td>Median “Core” MRI</td>
<td>MRI 6.8-11.7 mL</td>
<td>8-13 mL</td>
<td>15 mL</td>
<td>60.2 mL</td>
</tr>
<tr>
<td></td>
<td>CT 10.9-17.1 mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Perfusion Deficit</td>
<td>52.5 mL</td>
<td>76-80 mL</td>
<td>79 mL</td>
<td>177.6 mL</td>
</tr>
<tr>
<td>Final Infarct Volume</td>
<td>NA</td>
<td>NA</td>
<td>74.7→48.4 mL</td>
<td>105.2 mL</td>
</tr>
<tr>
<td>Infarct Growth</td>
<td>-0.9 mL-0.5 mL</td>
<td>24 Hr: 3-14 mL; D90: 2-12 mL</td>
<td>5.6 mL</td>
<td>24.1 mL</td>
</tr>
<tr>
<td>Revascularization</td>
<td>NA</td>
<td>24 Hr: 58-88%*</td>
<td>DSA: 46%†</td>
<td>DSA Emb.: 67%‡, 27%†, D7 All: 78%</td>
</tr>
<tr>
<td>Mean mRS</td>
<td>NA</td>
<td>NA</td>
<td>3.1</td>
<td>3.85</td>
</tr>
<tr>
<td>mRS 0-2</td>
<td>53%</td>
<td>44-84%</td>
<td>39%</td>
<td>19%</td>
</tr>
</tbody>
</table>

*Any TIMI Improvement, †TICI 2b-3, TICI 2a-3‡
Conclusions

• While no trial to date has definitively proven imaging selection hypothesis, positive results from TNK, DEFUSE 2, and secondary DIAS-2 analyses are encouraging
  ➢ Low recanalization rates and large infarct cores in MR RESCUE may explain negative results and differences compared to DEFUSE 2

• Studies support role for target vessel imaging as a potentially important selection biomarker for reperfusion therapies

• Trials including both MRI and CT suggest techniques as currently applied are not comparable for penumbral prediction

• Trial designs differed making extrapolation of results from one to another problematic
  ➢ Differences in cohort characteristics are a concern and raise the issue of enrollment biases
  ➢ TNK and DEFUSE 2 provide supportive data for penumbral imaging selection, but DEFUSE 2 lacked standard medical care control arm and TNK lacked non-penumbral arm
Lessons from Studies to Date

- Imaging selection biomarkers may need to be better validated in controlled trials prior to implementation as selection criteria.
- Standardization of imaging approaches as well as outcome measures and timepoints are needed to allow comparison across studies.

Future Directions

- Imaging selection, particularly for stroke treatments in late time windows, remains promising.
- Further randomized, controlled trials are needed to test the full spectrum of the imaging selection biomarkers for both intravenous therapies and new generation stent-retriever devices.
Thank You