TEsting Multiple PrehOspital therapies - Emergency Management of Stroke (TEMPO-EMS)

Nerses Sanossian
David Hess
William Meurer
Jeffrey Saver
Caitlyn Ellerbe
on behalf of the TEMPO-EMS Investigators
Overview

• Introduction: current state of prehospital stroke research
• Background/Rationale
• Methods
• Agents to be Tested
• Major Trial Questions
• Summary
## Prehospital Stroke Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Intervention</th>
<th>Strategy</th>
<th>Design</th>
<th>Size</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAST-MAG Pilot</td>
<td>Magnesium</td>
<td>NP</td>
<td>Historical controls</td>
<td>20</td>
<td>2004</td>
</tr>
<tr>
<td>Helsinki EMS</td>
<td>IV + SQ Insulin</td>
<td>Homeostasis</td>
<td>Randomized open / hist cont</td>
<td>23</td>
<td>2011</td>
</tr>
<tr>
<td>Aarhus University</td>
<td>Remote perconditioning</td>
<td>NP</td>
<td>Randomized open label</td>
<td>443</td>
<td>2014</td>
</tr>
<tr>
<td>RIGHT</td>
<td>Glyceryl trinitrate</td>
<td>BP, MP</td>
<td>Randomized open label</td>
<td>41</td>
<td>2014</td>
</tr>
<tr>
<td>PIL-FAST</td>
<td>Lisinopril</td>
<td>BP</td>
<td>Randomized open label</td>
<td>14</td>
<td>2014</td>
</tr>
<tr>
<td>FAST-MAG Pivotal</td>
<td>Magnesium</td>
<td>NP</td>
<td>Randomized, blinded placebo</td>
<td>1700</td>
<td>2015</td>
</tr>
<tr>
<td>RIGHT 2</td>
<td>Glyceryl trinitrate</td>
<td>BP, NP</td>
<td>Randomized open label</td>
<td>850</td>
<td>Recruiting</td>
</tr>
<tr>
<td>FRONTIER</td>
<td>NA-1</td>
<td>NP</td>
<td>Randomized blinded placebo</td>
<td>558</td>
<td>Recruiting</td>
</tr>
</tbody>
</table>
# FAST-MAG Time Intervals

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=843)</th>
<th>Magnesium (n=857)</th>
<th>Total (n=1700)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset* to Drug (mins)</td>
<td>46 (36-62)</td>
<td>45 (35-60)</td>
<td>45 (35-62)</td>
<td>0.24</td>
</tr>
<tr>
<td>Onset to Drug (categorical)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1 hours</td>
<td>73.2%</td>
<td>75.3%</td>
<td>74.3%</td>
<td>0.61</td>
</tr>
<tr>
<td>1-2 hours</td>
<td>25.7%</td>
<td>23.7%</td>
<td>24.7%</td>
<td></td>
</tr>
<tr>
<td>&gt;2 hours</td>
<td>1.1%</td>
<td>0.9%</td>
<td>1.0%</td>
<td></td>
</tr>
<tr>
<td>On Scene to Drug</td>
<td>23 (19-28)</td>
<td>23 (18-27)</td>
<td>23 (18-27)</td>
<td>0.58</td>
</tr>
<tr>
<td>On Scene to Door**</td>
<td>33 (27-39)</td>
<td>32 (27-39)</td>
<td>33 (27-39)</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Onset to on-scene: 23 min
Onset to ED arrival: 58 min
Onset to TPA: 137 min
Onset to Endovascular: 275 min

Onset to NP: 45 min
NP to ED arrival: 13 min
NP to TPA: 92 min
NP to Endovascular: 230 min

*Onset = last known well time
**Historical comparator, pretrial LA scene to door times = 35 minutes (Stroke 2004;35:e106-108)

Supported by NIH-NINDS
Background

• Neuroprotection started in the field is possible
• Earlier treatment is likely to be better
• Neuroprotection better with recanalization
• There are many promising NP agents
  – Not all are testable in the field
  – How to select those that are most likely to succeed in clinical trials
• Novel approaches are needed going forward
How to Select the Best Agents

Potential Agents
- Glyceryl Trinitrate (nitroglycerine)
- Remote Ischemic Conditioning
- Minocycline
- NA-1
- Valproic Acid
- Progesterone
- NXY-059
- Uric Acid
- Statin
- Tirilizad
- Saline/iced saline
- Hypothermia
- Xenon
- Normobaric Hyperoxia
- 3K3 A-activated protein C (APC)
- Others

Desired Characteristics
- Safe in intracerebral hemorrhage
- Ease of administration & preparation in the field
- Preclinical data indicates efficacy in ischemic stroke
- No interaction with tPA
- Clinical/experimental data demonstrating increasing efficacy with earlier administration
- No need for infusion pump, infused via gravity
- Drug/device is readily available from manufacturer
- CNS penetration
- Meets current STAIR preclinical development criteria
- Methods for prep and administration are within usual skill set of paramedics
- Ease of storage in the field within ambulance conditions (wide range of temperature, no need for refrigeration or frequent swap-out)
Three Agents with Scientific Rationale for Prehospital Administration

- Remote Ischemic Conditioning (RIC)
- Minocycline
- Glyceryl Trinitrate (GTN, nitroglycerine)
Scientific Premise For A Trial To Evaluate Remote Ischemic (RIC)

- **Mechanism of Action:** RIC targets multiple pathways and triggers an “ischemic tolerant” phenotype.
- **Preclinical stroke studies in rodents**
  - Protective in thromboembolic clot and mechanical models of males, females, aged
  - Increases CBF
- **RIC in STEMI trials show reduction of myocardial infarct size**
  - CONDI trial Randomized prehospital trial as adjunct to PCI in Denmark (Botker, Lancet 2010)
  - ERIC LYSIS Randomized hospital trial of RIC as adjunct to thrombolysis in Mauritius showed reduction of infarct size (troponin)
  - CONDI and CRISP (adjunct to elective PCI) show RIC x 1 associated with long term (5-6 yr) reduction of MACCE
    - Studies highlight that RIC targets reperfusion injury and potential as adjunct to tPA and MT
  - Danish randomized prehospital trial of RIC in acute stroke (Hougaard et al Stroke 2014)
- **Safety established in clinical studies of ACS and stroke**
Scientific Premise for Minocycline

• Multiple mechanisms of action  
  – MMP-9 inhibitor  
  – PARP inhibitor  
  – Anti-inflammatory (anti-microglial)  
  – Scavenger of peroxynitrite

• Preclinical studies showing benefit in mechanical and thromboembolic models AND in ICH models  
  – Effective with tPA  
  – Reduces tPA-related ICH  
  – Allows tPA to be given later and be effective  
  – MINO active in ICH models

• Safety in clinical studies
Scientific Premise for GTN

• Multiple mechanisms
  – NO donor
  – Cerebral vasodilator (HA)
  – Lowers BP ~ 10 mm Hg
• Preclinical models better with earlier admin
  – Studies across NO donors
• Clinical: better outcomes with earlier admin
  – ENOS <6 hour OR 0.51 (95%CI, 0.32–0.80)*
    • ENOC <6 hours ICH OR 0.22 (95%CI 0.07-0.69)*
    – RIGHT 1-point improvement on mRS (0.040)
• Safety established (ENOS >4000 cases)

* Shift in modified Rankin scale
Adaptive Clinical Trial Design

• There is no single consensus candidate agent
• Need a mechanism to look at multiple agents concurrently in Phase 2
  – More cost effective
  – Test agents with different modes of action
  – Elimination of agents early
Methods

• Bayesian multi-arm multi-stage (MAMS) Phase 2B randomized controlled clinical trial of three treatments (a) transdermal glyceryl trinitrate (GTN), (b) minocycline, and (c) remote ischemic conditioning (RIC), initiated by paramedics in the field within 2 hours of symptom onset in 900 patients with suspected acute stroke
Overview

• Primary objective: to evaluate the efficacy and safety of field-initiated glyceryl trinitrate (GTN), minocycline, and remote ischemic conditioning (RIC) in improving the long-term functional outcome of patients with acute stroke
• Subjects will be recruited in the field via exception from informed consent (EFIC) mechanism
• Each ambulance will be stocked with one case containing either
  – (a) a transdermal drug delivery system (containing GTN 5mg/24 hours or placebo)
  – (b) a 100cc bag of saline to run over gravity (containing a fixed dose of 400 mg minocycline or multi-vitamin placebo for color match)
  – (c) a brachial RIC device (pre-set to 220 mm/Hg for active and no inflation for sham )
• Treatment allocation will be predetermined and ambulances will be carrying only the assigned intervention
• Allocation will be 1:1:1:1 for each treatment arm or placebo.
Key Points

• Transdermal GTN or placebo patch will remain in place for 24 hours, infusion of minocycline/vitamin will be over 1 hour with no further therapy and the RIC device will stay with the subject for 24 hours

• All subjects are eligible for TPA and neuro-interventional procedures

• Follow-up assessments will be performed at ED arrival, 24 hours, day of discharge, and day 90.
Inclusion/Exclusion

Key Inclusion
• Suspected stroke identified with the modified Los Angeles Prehospital Stroke Screen (LAPSS)
• Age >40
• Last known well time within 2 hours of treatment initiation
• Deficit present for > 15 minutes
• Systolic blood pressure 120-220 mm Hg

Key Exclusion
• Coma [GCS ≤8]
• Rapidly improving neurologic deficit
• Pre-existing disease that would confound the neurological or functional outcome evaluations
• Severe respiratory distress (O2 sat < 90% or respiratory rate < 12 or > 24)
• Major head trauma in the last 24 hours
• Recent stroke within prior 30 days
• Use of erectile dysfunction therapies in the previous 48 hours
Total Sample Size
Phase II Design

• Assume 25% of total sample from Phase III design
  – N = 600 total; N = 150 per arm
  – Two interim analyses for efficacy/futility
Current Analysis

\[ P[(\pi_T - \pi_c) > 5\%] < 30\% \]

• Interpretation:
  – Arm will stop for lack of substantial promise if there is less than 30% chance that the treatment difference is greater than 5%

• Primary outcome in ischemic stroke
  – We will enroll approximately 900 subjects to get 600 cases of ischemic stroke
Percent of Trials Stopping for Lack of Substantial Promise

Futility: \( P(\Delta > 5\%) \leq C_F \)

<table>
<thead>
<tr>
<th>Tx</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx 1 (50%)</td>
<td>48.1</td>
<td>65.5</td>
<td>75.0</td>
</tr>
<tr>
<td>Tx 2 (55%)</td>
<td>27.1</td>
<td>38.3</td>
<td>46.0</td>
</tr>
<tr>
<td>Tx 3 (60%)</td>
<td>13.5</td>
<td>17.5</td>
<td>19.7</td>
</tr>
</tbody>
</table>
StrokeNet

• Sites that have experience with prehospital emergency trials
  – NETT
  – ROC
• Established relationships with EMS agencies
• Experience with use of EFIC
  – FDA approval
  – Regional approval
Summary

• Prehospital with start <2 hours
  – Majority <1 hour
• Target 600 Ischemic Stroke cases
  – Estimate 900 enrolments (100 mimic, 200 ICH)
• EFIC
  – Explicit consent after arrival
• Minimize impact on other clinical trials
BACK UP SLIDES
Rationale RIC and MINO

• Single targets have not worked in stroke
• Need to target multiple targets and pathways (STAIR)
  – Target CBF and collaterals (RIC)
• Need to test agents/devices in combination with tPA
• Mino and RIC have “activity” against both ischemic stroke and ICH
• Both interventions are “mega-safe”
• Both feasible in ambulance
  – Mino: one IV dose over an hour (half life of 24 hrs)
  – RIC: done in ambulance in Denmark for MI and stroke and in ED for MI(thrombolysed) in Mauritius
Features of this pre-clinical study

(Hoda et al Exp Transl Stroke Med. 2014 Jun 21;6:8)

• Use of thromboembolic autologous clot model (most physiological)
• 12 month old mice (“middle age”)
• Administer IV tPA “late” at 4 hours
• Measurement of CBF (LSCI)
• 2 x 2 factorial design: randomized, blinded, outcomes of infarct size and functional outcome
• Short term outcome (48 hrs)
Infarct size at 48 hours by TTC staining
Functional outcome: NDS and adhesive tape

CBF by LSCI
Summary of Results

• CBF increased with RIC (seen in all our models)

• RIC and MINO both effective in non-tPA- and tPA (late at 4 hrs)= treated mice

• Additive effect of RIC and MINO on infarct size (significant) and functional outcome (trend)
Danish prehospital trial of RIC in acute stroke
Hougaard KD, Stroke 2014;45

- Randomized to rPerC or no treatment in ambulance
- Primary outcome of penumbral salvage
  No difference between groups
- Voxel based analysis of “tissue at risk” in favor of rPerC
- Low baseline NIHSS (mean 5)
- Most patients did not receive full regimen
- Suggestion of “activity”