Intravenous thrombolysis
State of Art

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Stroke Unit.
Hospital Vall d´Hebron
Barcelona
## Independent predictors of good outcome after iv tPA

<table>
<thead>
<tr>
<th>Factor</th>
<th>SE</th>
<th>OR (95%CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>0.467</td>
<td>(0.69)</td>
<td></td>
</tr>
<tr>
<td>Recanalization</td>
<td>1.41</td>
<td>(0.26) 4.11 (2.42-6.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>-1.03</td>
<td>(0.4) 0.35 (0.16-0.78)</td>
<td>0.0013</td>
</tr>
<tr>
<td>ASPECTS value</td>
<td>1.09</td>
<td>(0.49) 2.98 (1.13-7.85)</td>
<td>0.0253</td>
</tr>
<tr>
<td>SBP</td>
<td>-1.12</td>
<td>(0.43) 0.32 (0.13-0.76)</td>
<td>0.0116</td>
</tr>
<tr>
<td>Proximal occlusion</td>
<td>-1.37</td>
<td>(0.45) 0.25 (0.10-0.61)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*CLOTBUST Collaborators*
Impact of recanalization on stroke outcome

Comparison: 01 Recanalization vs. Non-Recanalization
Outcome: 04 Good Outcome by Time

<table>
<thead>
<tr>
<th>Study</th>
<th>Recanalization n/N</th>
<th>Non-Recanalization n/N</th>
<th>Peto OR (95%CI Fixed)</th>
<th>Weight %</th>
<th>Peto OR (95%CI Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Recanalization within 6 hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>von Kummer 1991</td>
<td>8 / 12</td>
<td>3 / 9</td>
<td>2.9</td>
<td>2.9</td>
<td>3.57[0.66,19.33]</td>
</tr>
<tr>
<td>Mobius 1991</td>
<td>6 / 14</td>
<td>0 / 4</td>
<td>1.6</td>
<td>1.6</td>
<td>6.18[0.63,61.08]</td>
</tr>
<tr>
<td>Casto 1992</td>
<td>4 / 4</td>
<td>0 / 1</td>
<td>0.3</td>
<td>0.3</td>
<td>148.41[1.11,19930.37]</td>
</tr>
<tr>
<td>Endo 1998</td>
<td>4 / 8</td>
<td>0 / 13</td>
<td>1.7</td>
<td>1.7</td>
<td>21.94[2.46,195.80]</td>
</tr>
<tr>
<td>Lewandowski 1999</td>
<td>9 / 14</td>
<td>2 / 8</td>
<td>2.9</td>
<td>2.9</td>
<td>4.48[0.82,24.47]</td>
</tr>
<tr>
<td>Alexandrov 2001</td>
<td>15 / 43</td>
<td>1 / 22</td>
<td>5.9</td>
<td>5.9</td>
<td>5.00[1.53,16.33]</td>
</tr>
<tr>
<td>Molina 2002</td>
<td>11 / 17</td>
<td>2 / 15</td>
<td>4.3</td>
<td>4.3</td>
<td>7.87[1.96,31.65]</td>
</tr>
<tr>
<td>Subtotal(95%CI)</td>
<td>57 / 112</td>
<td>8 / 72</td>
<td>19.7</td>
<td>19.7</td>
<td>6.36[3.32,12.17]</td>
</tr>
</tbody>
</table>

Test for heterogeneity chi-square=3.68 df=6 p=0.72
Test for overall effect z=5.58 p<0.00001

Rha, Saver, Stroke 2007
Quantitative trends over time in reperfusion rates in active arms of recanalization trials

Patel, Saver. Stroke 2013
Impact of Onset-to-Reperfusion Time on Stroke Mortality
A Collaborative Pooled Analysis

Mikael Mazighi, MD, PhD; Saqib A. Chaudhry, MD; Marc Ribo, MD; Pooja Khatri, MD, MSc; David Skoloudik, MD; Maxim Mokin, MD; Julien Labreuche, BST; Elena Meseguer, MD; Sharon D. Yeatts, PhD; Adnan H. Siddiqui, MD; Joseph Broderick, MD; Carlos A. Molina, MD; Adnan I. Qureshi, MD; Pierre Amarenco, MD


480 patients with endovascular treatment & known time of reperfusion

For each +30 min to reperfusion - 10% chances of favorable outcome
“Time is brain” also means “time is clot”
Benefit to Risk ratio in randomized acute stroke trials

![Graph showing benefit to risk ratio over time to intervention in acute stroke trials. The graph includes various trials such as TAAIS, Tenecteplase, Synthesis Expansion, CLOTBUST, and others. Each trial is plotted based on the benefit to risk ratio and time to intervention.]
Use of tPA in real world

• Patients > 80y
• Minor stroke
• Body weight > 100 kg
• Without occlusion
• < 3h without mismatch
• Previous Aco, normal INR
• NOAC and normal coagulation
Challenges in reperfusion therapy

- Improve access to treatment
- Extend therapeutic window
- Non-pharmacological reperfusion strategies
- Increase recanalization rates
- Shortening pre- and inhospital delays
Improving early access to treatment

“Golden hour” < 60 min
“Diamond hour” < 30 min
Improving access and early treatment

- Increase awareness
- Telemedicine, telethrombolysis
- Prehospital thrombolysis
- Shortening DTN times
Potencial: 300 - 500 consultes / any

2008-2012

Hospitals amb:
>100 ictus/any
>40 km del centre de referència
TAC disponible 24 hores
Potencial: >1000 consultes / any

Figueres
Palamos
Girona
Mataró
Germans Trias
Vic
Granollers
Vall d’Hebron
Lleida
Tremp
Bellvitge
Igualada
Manresa
Vilafranca
Garaf
Mora
Different approaches of pre- and in-hospital stroke management

Improving *early* access to treatment
Neurologist
Paramedic
Radiographer
CT scan
Point-of-care Lab
Teleradiology
Prehospital Thrombolysis
PHANTOM-S pilot study

- 152 patients treated, 23 received tPA

<table>
<thead>
<tr>
<th></th>
<th>STEMO</th>
<th>CONTROL</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>23</td>
<td>50</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Call-to-needle time:</td>
<td>62 min</td>
<td>98 min</td>
</tr>
<tr>
<td>On site-to-needle time:</td>
<td>48 min</td>
<td>91 min</td>
</tr>
<tr>
<td>SICH</td>
<td>2(9%)</td>
<td>3(6%)</td>
</tr>
<tr>
<td>Potentials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reducing time to tPA treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Earlier start of general stroke treatment, e.g., neuroprotectants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Earlier start of stroke subtype-specific treatment beyond tPA, e.g., warfarin reversal or BP lowering in intracerebral hemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Routing of patients suitable for endovascular or neurosurgical therapies to appropriate receiving hospitals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comprehensive prenotification of in-hospital facilities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effective management of “golden hour” trials in acute stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous stroke awareness campaign with high visibility</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recognition of stroke patients at dispatcher level is desirable but limited by scarce information in emergency calls</td>
</tr>
<tr>
<td>Major infrastructural changes needed, e.g., training of dispatchers and paramedics, significant modifications of rescue algorithms</td>
</tr>
<tr>
<td>Diagnostic accuracy may be weakened by the short observation times</td>
</tr>
<tr>
<td>High costs for CT-equipped ambulances (investment and staffing) require frequent use, thus limiting utilization in rural areas</td>
</tr>
<tr>
<td>Safety and efficacy of current approaches not yet shown in sufficiently powered studies</td>
</tr>
</tbody>
</table>

Abbreviations: BP = blood pressure; tPA = tissue plasminogen activator.
Improving time delays in the rescue chain

• Improve stroke awareness in the population
• Optimize advanced prenotification (stroke code)
• Continuous EMS personnel training
• Telemedicine with video examination (TeleStroke)
• Development of rapid diagnostic algorithms
  – Ultrasound
  – Portable CT scan
  – Telemedicine-assisted rapid identification and direct transfer to hospital CT scan
Shortening Door-to-needle times

From: Door-to-Needle Times for Tissue Plasminogen Activator Administration and Clinical Outcomes in Acute Ischemic Stroke Before and After a Quality Improvement Initiative
A Simple Text-Messaging Intervention Is Associated With Improved Door-to-Needle Times for Acute Ischemic Stroke

Molly M. Burnett, MD; Lara Zimmermann, MD; Zlatan Coralic, PharmD; Tina Quon, RN, MSN, CEN, BC; William Whetstone, MD; Anthony S. Kim, MD, MAS

Background and Purpose—Timely administration of intravenous tissue-type plasminogen activator (IV tPA) is associated with improved outcomes for acute ischemic stroke; yet, developing processes to consistently provide prompt treatment remains a challenge. We developed and evaluated a simple quality improvement intervention designed to improve door-to-needle (DTN) times for resident-led Code Stroke teams at an academic medical center.

Methods—We evaluated a simple text-messaging based intervention with real-time feedback to improve DTN times for intravenous tissue-type plasminogen activator. We used the rank-sum test and linear regression to evaluate for a change in DTN times that was temporally associated with the rollout of the intervention.

Results—A total of 202 patients received intravenous tissue-type plasminogen activator; 94 preintervention and 108 postintervention. The median DTN time was significantly lower in the postintervention period (56 minutes [interquartile range 44–71] versus 82 minutes [IQR 68–103], P<0.0001) and a significantly higher proportion of patients were treated within 60 minutes (61% versus 16%, P<0.001).

Conclusions—A simple real-time text-messaging intervention was associated with a significant improvements in DTN times for acute ischemic stroke. (Stroke. 2014;45:00-00.)

Key Words: door-to-treatment time □ quality improvement □ stroke □ thrombolytic therapy
Door-to-needle times before and after text-messaging-based quality improvement
Estela Sanjuan:
Vamos bajando! Nos vemos abajo
09:56

Mariam: 
oks
bajando a por tupper
09:57

David Rodr...
13 de noviembre de 2013
10:09

Sandra Bonet:
Hace una hora hemip izq y disartria
06:49

Alan:
Igual lo hacemos arriba jorge para no moverla demasiado
Ok sandra avisanos
06:52

NIH 11, TIBI 3 a 45mm, occlusion distal, bajamos TC
07:23 OK Probable Clotbuster
07:24

Jorge Pagola:
Nombre y locus del código
07:57

Alan:
Donde están?
08:03

Marc... 10:47

Marc Ribo:
Igual esperamos un poco
10:49
• Improve prenotification
• Shorten time to evaluation
• Improve inhospital coordination
• Speed up decisión making
• Improve training
Hello 911

yes, what's your emergency

two girls are fighting for me

what is the problem with it sir

the ugly one is winning.
Video monitoring of stroke thrombolysis

- ER Arrival
- Blood Sample
- NIHSS
- TCD
- BP
- Departing VM_Box
CT-tPA
ITN time is a much greater source of variability in hospital DTN times – common contributor to delays in timely tPA therapy.

More attention is needed to determine systems changes that can decrease ITN time for patients with acute ischemic stroke.
Extend the window beyond 4.5h

Time is brain
CT-based thrombolysis

Selection
MRI / CTP
Extending window beyond 4.5h

Time is brain
CT-based thrombolysis

Selection
MRI / CTP

Adjusted odds ratio vs OTT (min)
Mismatch concept

Molina C, Saver J, Stroke 2005
Desmoteplase In Acute Stroke

Reperfusion  PWI reduction $\geq 30\%$ or TIMI change $\geq 2$ post-thrombolysis)
Responder rate DIAS/DEDAS & DIAS 2

<table>
<thead>
<tr>
<th>Group</th>
<th>DIAS/DEDAS</th>
<th>DIAS-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>25%</td>
<td>30%</td>
</tr>
<tr>
<td>90 µg/kg</td>
<td>45%</td>
<td>45%</td>
</tr>
<tr>
<td>125 µg/kg</td>
<td>60%</td>
<td>55%</td>
</tr>
</tbody>
</table>
Responder rate DIAS/DEDAS & DIAS 2

- Lower NIHSS score
- Lower rate of TIMI 0-1

Graph showing responder rate (%) for different treatments:

- Placebo
- 90 µg/kg
- 125 µg/kg

Bars represent DIAS/DEDAS and DIAS-2.
Responder rate DIAS/DEDAS & DIAS 2

- Lower NIHSS score
- Lower rate of TIMI 0-1
- Higher mortality

<table>
<thead>
<tr>
<th></th>
<th>DIAS/DEDAS</th>
<th>DIAS-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90 µg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>125 µg/kg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bar chart showing responder rates for different doses (Placebo, 90 µg/kg, 125 µg/kg).
Focusing on vascular status
ECASS 4 - EXTEND

- Iv tPA 3-9 hours
- Penumbra-based trial
  PWI > 100% DWI
- Ongoing. Europe and Australia
WAKE-UP

• Age 18-80 years
- Treatment can be started within 4.5 hours of symptom recognition (e.g., awakening)
- MRI showing a pattern of "DWI-FLAIR-mismatch", 

![Image of MRI scans showing DWI-FLAIR mismatch and no mismatch]
Improving the efficacy profile of thrombolysis
Improving the efficacy profile of thrombolysis
Tenecteplase (TNK)

- Longer half-life
- 14 times more fibrin-specific
- More resistant to PAI-1
Continuous TCD monitoring

Molina et al ISC New Orleans 2008
Temporal profile of tPA- and TNK-induced recanalization

Molina et al ISC New Orleans 2008
2h-recanalization on TCD

<table>
<thead>
<tr>
<th></th>
<th>tPA</th>
<th>TNK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>33</td>
<td>43</td>
</tr>
<tr>
<td>Partial</td>
<td>20</td>
<td>26</td>
</tr>
<tr>
<td>No</td>
<td>48</td>
<td>31</td>
</tr>
</tbody>
</table>

P = 0.014
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.

Coordinating Centre: John Hunter Hospital, Newcastle

 Participating Centres: Royal Melbourne Hospital, Box Hill Hospital
Tenecteplase versus alteplase for acute ischaemic stroke: phase II study

• **Hypotheses:**
  – TNK superior to tPA for early reperfusion and early neurologic improvement

• **Summary of study design:**
  – Acute stroke onset within 6 hours with vessel occlusion + ischaemic penumbra on multimodal CT.
  – Central randomisation: patients to receive 0.9 mg/kg tPA or TNK (0.1 mg/kg or 0.25 mg/kg).
  – Dual primary outcomes at 24 hours
    1. Extent of early reperfusion
    2. Extent of early clinical improvement.
Advanced imaging-based selection and outcome assessment

1. Identify pts most likely to respond (‘enriched’ population)
2. Measure treatment response – biologic marker/proof of concept

1. Selection at Baseline

Reperfusion

Treatment target (small core + penumbra)

+ 

Treatment target (vessel occlusion)

2. Outcome assessment at 24 h

No reperfusion

Imaging Outcomes
Primary outcome = reperfusion from pre-treatment CT perfusion lesion to 24 hour MR perfusion lesion
Secondary outcomes = infarct growth, ICH

Dual Target Selection

Penumbra
Infarct core
Table 1. Characteristics of the Patients at Baseline.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Alteplase (N = 25)</th>
<th>Tenecteplase (N = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>0.1 mg/kg</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age — yr</td>
<td>70±8.4</td>
<td>72±6.9</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>12 (48)</td>
<td>13 (52)</td>
</tr>
<tr>
<td>Hypertension — no. (%)</td>
<td>15 (60)</td>
<td>16 (64)</td>
</tr>
<tr>
<td>Diabetes mellitus — no. (%)</td>
<td>1 (4)</td>
<td>8 (32)</td>
</tr>
<tr>
<td>Blood glucose — mmol/liter</td>
<td>6.4±1.1</td>
<td>7.1±2.0</td>
</tr>
<tr>
<td>Hyperlipidemia — no. (%)</td>
<td>9 (36)</td>
<td>13 (52)</td>
</tr>
<tr>
<td>Atrial fibrillation — no. (%)</td>
<td>6 (24)</td>
<td>9 (36)</td>
</tr>
<tr>
<td>Current smoking — no. (%)</td>
<td>1 (4)</td>
<td>9 (36)</td>
</tr>
<tr>
<td>Current medications — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet agent</td>
<td>11 (44)</td>
<td>11 (44)</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>NIHSS score†</td>
<td>14.0±2.3</td>
<td>14.5±2.3</td>
</tr>
<tr>
<td>Time to treatment — hr</td>
<td>2.7±0.8</td>
<td>3.1±0.9</td>
</tr>
</tbody>
</table>

Parsons et al NEJM 2012
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Alteplase (N = 25)</th>
<th>Tenecteplase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.1 mg/kg (N=25)</td>
<td>0.25 mg/kg (N=25)</td>
</tr>
<tr>
<td><strong>Imaging</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume of infarct core — ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>2–41</td>
<td>1–25</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>2–41</td>
<td>1–25</td>
</tr>
<tr>
<td>Volume of perfusion lesion — ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>76</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>21–185</td>
<td>22–199</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>21–185</td>
<td>22–199</td>
</tr>
<tr>
<td>Occlusion site — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior cerebral artery</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Proximal section of first segment of</td>
<td>11 (44)</td>
<td>6 (24)</td>
</tr>
<tr>
<td>middle cerebral artery</td>
<td>2 (8)</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Midsection of first segment of</td>
<td>5 (20)</td>
<td>10 (40)</td>
</tr>
<tr>
<td>middle cerebral artery</td>
<td>2 (16)</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Distal section of first segment of</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>middle cerebral artery</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Terminal internal carotid artery</td>
<td>2 (8)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>None</td>
<td>2 (8)</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>
Table 2. Study Outcomes in the Alteplase and Pooled Tenecteplase Groups.*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Alteplase (N=25)</th>
<th>Tenecteplase (N=50)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary imaging efficacy outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reperfusion at 24 hr — %†</td>
<td>55.4±38.7</td>
<td>79.3±28.8</td>
<td>0.004</td>
</tr>
<tr>
<td>Primary clinical efficacy outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improvement in NIHSS score between baseline and 24 hr‡</td>
<td>3.0±6.3</td>
<td>8.0±5.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- Link between imaging and clinical outcomes was very strong in our phase II study as we selected patients most likely to benefit from effective reperfusion.
Individual dose tier analysis
Co Primary Outcomes

Distribution of reperfusion

Distribution of change in NIHSS

Parsons et al NEJM 2012
TASTE

Tenecteplase versus Alteplase for Stroke Thrombolysis Evaluation
Objectives

• Test the hypothesis that patients with acute hemispheric ischaemic stroke who have a penumbra on perfusion CT or MRI within 4.5 hours of symptom onset will have less disability at 3 months when treated with IV tenecteplase (TNK) compared to IV alteplase (tPA).
Thrombolysis eligible patient stroke onset <4.5 hours

NCCT/CTP/CTA or MRI (DWI/PWI/MRA)

Core on DWI/CTP < 70 mL

Penumbra Mismatch Ratio > 1.8 (Tmax+6s) and > 15mL

Randomised to IV tPA (0.9 mg/kg) or IV TNK (0.25 mg/kg)

(Randomisation stratified by presence of ICA occlusion and infarct core volume)

Primary outcome = mRS 0-1 at 3 months

PROBE design. Sample size 1024.
Study Design

• 1024 patients will be recruited into the trial from 50-60 centres worldwide.

• 1st 200 patients mandatory reperfusion sub-study
  – Mandatory perfusion imaging (CT/MR) at 24 hours
  – Interim analysis of reperfusion and early clinical improvement (as per phase II study) TNK vs tPA
Study Endpoints

• Primary Outcome
  – modified Rankin Scale (mRS) 0-1 at 3 months

• Interim Analysis after 200 patients
  – Reperfusion at 24 hours
  – Early clinical improvement (reduction in acute – 24 hour NIHSS score)
  – mRS 0-1 at 3 months
Study Endpoints

• Safety:
  – Symptomatic intra-cerebral haemorrhage (sICH)
  – Death due to any cause
  – mRS 5-6 at 3 months
Some (of the more athletic members) of the TASTE team
US-Enhanced Thrombolysis

CLOTBUST Trial: Complete MCA Recanalization

- 27%
- 38%
- 13%
- 13%

p=0.03

### Meta-analysis of US-enhanced thrombolysis

Complete recanalization

#### 1.4.1 Sonothrombolysis TCD

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sonothrombolysis + rtPA</th>
<th>rtPA alone</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events *</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Alexandrov AV 2004</td>
<td>24</td>
<td>63</td>
<td>8</td>
</tr>
<tr>
<td>Molina 2006</td>
<td>36</td>
<td>75</td>
<td>8</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>60</td>
<td>138</td>
<td>99</td>
</tr>
</tbody>
</table>

- Total events: 60
- 16
- Heterogeneity: $\text{Tau}^2 = 0.00$; $\text{Chi}^2 = 0.17$, $df = 1$ ($P = 0.68$); $I^2 = 0$
- Test for overall effect: $Z = 4.02$ ($P = 0.00001$)

#### 1.4.2 Sonothrombolysis TCCD

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sonothrombolysis + rtPA</th>
<th>rtPA alone</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Eggers 2003</td>
<td>3</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>Eggers 2008</td>
<td>0</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Laure 2007</td>
<td>4</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>7</td>
<td>26</td>
<td>29</td>
</tr>
</tbody>
</table>

- Total events: 7
- 8
- Heterogeneity: $\text{Tau}^2 = 0.00$; $\text{Chi}^2 = 0.06$, $df = 1$ ($P = 0.81$); $I^2 = 0$
- Test for overall effect: $Z = 0.24$ ($P = 0.81$)

**Total (95% CI)**

<table>
<thead>
<tr>
<th>Total</th>
<th>164</th>
<th>128</th>
<th>100.0%</th>
<th>2.97 [1.67, 5.27]</th>
</tr>
</thead>
</table>

- Total events: 67
- 24
- Heterogeneity: $\text{Tau}^2 = 0.00$; $\text{Chi}^2 = 2.62$, $df = 3$ ($P = 0.45$); $I^2 = 0$
- Test for overall effect: $Z = 3.72$ ($P = 0.0002$)
- Test for subgroup differences: Not applicable

Tsivgoulis, et al. Stroke 2009
Meta-analysis of US-enhanced thrombolysis

Long-term outcome

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sonothrombolysis + rtPA</th>
<th>rtPA alone</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>1.6.1 Sonothrombolysis TCD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alexandrov AV 2004</td>
<td>22</td>
<td>53</td>
<td>14</td>
</tr>
<tr>
<td>Molina 2006</td>
<td>30</td>
<td>75</td>
<td>9</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td>128</td>
<td>85</td>
</tr>
<tr>
<td>Total events</td>
<td>52</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00, Chi² = 0.04, df = 1 (P = 0.85); I² = 0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.04 (P = 0.04)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 1.6.2 Sonothrombolysis TCCD |         |       |         |       |        |                                   |
| Eggers 2003          | 3       | 11    | 0       | 14    | 3.6%  | 11.94 [0.55, 260.26]               |
| Eggers 2008          | 1       | 7     | 0       | 5     | 3.0%  | 2.54 [0.09, 75.76]                 |
| Subtotal (95% CI)    |         | 18    | 19      | 6.5%  |        | 5.93 [0.61, 58.14]                 |
| Total events         | 4       |       | 0       |       |        |                                    |
| Heterogeneity: Tau² = 0.00, Chi² = 0.44, df = 1 (P = 0.51); I² = 0% |
| Test for overall effect: Z = 1.53 (P = 0.13) |

Total (95% CI) | 146 | 104 | 100.0% | 2.02 [1.13, 3.63]
Total events | 56 | 23 |        |                                    |
Heterogeneity: Tau² = 0.00, Chi² = 1.40, df = 3 (P = 0.71); I² = 0% |
Test for overall effect: Z = 2.37 (P = 0.02) |
Test for subgroup differences: Not applicable
### Meta-analysis of US-enhanced thrombolysis Risk of ICH

#### 1.2.1 Sonothrombolysis TCD

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sonothrombolysis + rtPA</th>
<th>rtPA alone</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alexandrov AV 2004</td>
<td>3 (63)</td>
<td>3 (63)</td>
<td>1.00 [0.19, 5.15]</td>
</tr>
<tr>
<td>Molina 2006</td>
<td>2 (75)</td>
<td>2 (36)</td>
<td>0.47 [0.06, 3.45]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>138 (99)</strong></td>
<td><strong>99</strong></td>
<td><strong>0.74 [0.21, 2.62]</strong></td>
</tr>
</tbody>
</table>

**Total events:** 5

Heterogeneity: $\tau^2 = 0.00; \chi^2 = 0.34, df = 1 (P = 0.56); I^2 = 0$

Test for overall effect: $Z = 0.47 (P = 0.64)$

#### 1.2.2 Sonothrombolysis TCCD

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sonothrombolysis + rtPA</th>
<th>rtPA alone</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eggers 2003</td>
<td>2 (11)</td>
<td>0 (14)</td>
<td>7.63 [0.33, 177.14]</td>
</tr>
<tr>
<td>Eggers 2008</td>
<td>1 (7)</td>
<td>0 (5)</td>
<td>2.54 [0.09, 75.76]</td>
</tr>
<tr>
<td>Laurre 2007</td>
<td>0 (9)</td>
<td>0 (11)</td>
<td>Not estimable</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>27 (30)</strong></td>
<td><strong>30</strong></td>
<td><strong>4.59 [0.46, 46.13]</strong></td>
</tr>
</tbody>
</table>

**Total events:** 3

Heterogeneity: $\tau^2 = 0.00; \chi^2 = 0.22, df = 1 (P = 0.64); I^2 = 0$

Test for overall effect: $Z = 1.29 (P = 0.20)$

**Total (95% CI):** 165 (129) 100.0% 1.13 [0.37, 3.42]

**Total events:** 8

Heterogeneity: $\tau^2 = 0.00; \chi^2 = 2.45, df = 3 (P = 0.48); I^2 = 0$

Test for overall effect: $Z = 0.21 (P = 0.84)$

Test for subgroup differences: Not applicable

Tsivgoulis, et al. Stroke 2009
CLOTBUST-ER

A Phase 3, Randomized, Placebo-Controlled, Double-Blind Trial of the Combined Lysis of Thrombus with Ultrasound and Systemic Tissue Plasminogen Activator (tPA) for Emergent Revascularization (CLOTBUST-ER) in Acute Ischemic Stroke.
Aim

to evaluate the efficacy of a novel transcranial ultrasound device and systemic tPA (Target group) compared to systemic tPA alone (Control group) in subjects with acute ischemic stroke.
CLOTBUST-ER CP-01 Study

• <80 y
• <time frame for tPA
• NIHSS > 10

Primary end-point: mRS 0-1
N=840; 1:1
CLOTBUSTER

- CLOTBUST-ER is ongoing with active enrollment at approximately 70 sites in 14 countries worldwide.

- 490 of 824 planned subjects have been enrolled to date., DSMB recommended continuation of the trial as planned without modification after the first interim analysis.
Conclusion

• Need to improve early access to tPA
  - Telemedicine
  - Prehospital thrombolysis
  - Shortening DNT

• Need to extend time window for tPA

• Need to develop more effective thrombolytics