THROMBECTOMY FOR STROKE
FIVE YEARS ANIVERSARY

What have we learned and where are we heading?

Tudor G. Jovin, M.D.
Professor and Chair
Department of Neurology
Cooper Medical School of Rowan University
Director, Cooper Neurological Institute
DISCLOSURES

Member steering committee/DSMB: Cerenovus-modest
Member DSMB: Brainsgate-modest
Principal Investigator DAWN, AURORA: Stryker Neurovascular
Consultant/Advisory Board: Ownership Interest: Silk Road Medical – modest
Consultant/Advisory Board: Ownership Interest: Blockade Medical-modest
Consultant/Advisory Board: Ownership Interest: FreeOx Biomedical-modest
Consultant/Advisory Board: Ownership Interest: Route 92-modest
Consultant/Advisory Board: Ownership Interest: Viz.ai-modest
Consultant/Advisory Board: Ownership Interest: Corindus
Consultant/Advisory Board: Anaconda- modest
Consultant: Medtronic-modest
patients died within 2 weeks, while six patients survived more than 6 weeks but less than 3 months. Only one patient survived a 1 year period. All the patients had severe neurologic deficits and died from secondary complications such as pulmonary thromboembolism, myocardial infarction, or pneumonia. These results parallel the experiences of others [1–4] in documenting the poor prognosis of basilar artery thrombosis. In our view, the standard regimen using heparin and other anticoagulants offered no proven therapeutic advantage. With this in mind, we felt challenged to develop a new therapy, despite the possible dangers involved.

The systemic administration of the fibrinolytic agent streptokinase in doses of 2,500,000 IU/day is reported to be hazardous and fraught with complications [5]. Moreover, this therapy cannot be applied soon after angiography because of the certainty of local bleeding. However, cardiologists [6–8] have demonstrated that in patients with coronary artery thrombosis, the local use of fibrinolytic agents is superior to systemic application and that even in high accompanied by low-dose heparin treatment calculated thrombin time by a factor of 2 or 3.

Case Reports

Case 1

A 27-year-old woman, after an initial transient headache and hemiataxia, experienced deterioration. Somnolence, tetraparesis, and multiple complications were present. The details have been described elsewhere [5]. Upper basilar occlusion was found (fig. 1A) in conjunction with a midline shift (fig. 1B). Intracranial vertebral artery occlusion. After administration of 200,000 IU streptokinase, recanalization was achieved (fig. 1C). Further angiographic improvement was observed the next day and normalization was achieved after a subsequent infusion of 70,000 IU streptokinase (fig. 1D). We belie

Fig. 1.—Case 1. A, Left vertebral angiogram (oblique projection). Basilar artery stenosis (arrows). B, Recanalization after local intraarterial fibrinolysis.
Intra-arterial Prourokinase for Acute Ischemic Stroke
The PROACT II Study: A Randomized Controlled Trial

90 day mRS 0-2: 40% r-proUK vs. 25% controls (p=.04)

Mortality: 25% r-proUK vs. 27% controls

Recanalization rates: 66% r-proUK vs. 18% controls

Symptomatic intracranial hemorrhage: 10% r-proU vs. 2% of controls
HISTORICAL PERSPECTIVE

MERCI – FDA approved 2004 (foreign body/clot removal)

PENUMBRA – FDA approved 2007 (foreign body/clot removal)
SECOND GENERATION THROMBECTOMY DEVICES

Solitaire (Covidien/Medtronic)
FDA approved (clot removal) 2012

Trevo (Covidien/Medtronic)
FDA approved (clot removal) 2012

FIRST GENERATION THROMBECTOMY TRIALS

Endovascular Therapy after Intravenous t-PA versus t-PA Alone for Stroke

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., Jeffrey R. Alger, Ph.D., Val Nenov, Ph.D., Zahra Ajan, 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 Wintemark, M.D., Judy Guzy, R.N., Sidney Starkman, M.D., and Jeffrey L. Saver, M.D., for the MR RESCUE Investigators*

Endovascular Treatment for Acute Ischemic Stroke — Still Unproven
Marc I. Chimowitz, M.B., Ch.B.
PROPOSED REASONS FOR FAILURE TO SHOW BENEFIT OF EVT IN IMS 3

1. No proof of vascular occlusion
2. Unfavorable imaging (large infarcts)
3. Slow workflow *
4. Inefficient revascularization **

* Median Iv t-PA to groin puncture 84 min, Goyal et al, Circulation 2014
** TICI 2b-3 reperfusion rates 42%, Tomsick et al., JNIS 2015

Nogueira et al (Stroke, 2013)
Every 30 minute delay in reperfusion associated with a 10% relative reduction in probability of good clinical outcome (mRS 0-2).
Results of the Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands

Diederik Dippel, Olvert Berkhemer, Puck Fransen, Debbie Beumer, Lucie van den Berg,
Hester Lingsma, Wim van Zwam, Robert van Oostenbrugge,
Aad van der Lugt, Yvo Roos and Charles Majoie,
for the MR CLEAN investigators
A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke


Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke


Stent-Retriever Thrombectomy after Intravenous t-PA vs. t-PA Alone in Stroke


Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection


Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke

Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials


<table>
<thead>
<tr>
<th>Overall</th>
<th>Key</th>
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<th>2</th>
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<td>Control population (n=645)</td>
<td>50</td>
<td>7.9</td>
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<td>Intervention population (n=633)</td>
<td>10.0</td>
<td>16.9</td>
<td>19.1</td>
<td>16.9</td>
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<table>
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<th>2</th>
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<td>Control population (n=80)</td>
<td>34</td>
<td>6.2</td>
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<td>Intervention population (n=108)</td>
<td>10.2</td>
<td>15.7</td>
<td>17.6</td>
<td>18.5</td>
<td>7.4</td>
<td>7.4</td>
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<table>
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<th>Received alteplase</th>
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<th>2</th>
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<td>Control population (n=565)</td>
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<td>8.1</td>
<td>13.8</td>
<td>17.5</td>
<td>23.7</td>
<td>13.3</td>
<td>18.4</td>
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<tr>
<td>Intervention population (n=575)</td>
<td>9.9</td>
<td>17.1</td>
<td>19.4</td>
<td>16.6</td>
<td>17.3</td>
<td>5.9</td>
<td>13.7</td>
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Overall Treatment Effect
Disability shift NNT = 2.6

Functional independence
NNT = 5
7.3 hour time window for EVT (unselected patients)

[Saver et al (JAMA, 2016)]
Fast Versus Slow Progressors of Infarct Growth in Large Vessel Occlusion Stroke
Clinical and Research Implications

Marcelo Rocha, MD, PhD; Tudor G. Jovin, MD
Prevalence and Temporal Distribution of Fast and Slow Progressors of Infarct Growth in Large Vessel Occlusion Stroke

Marcelo Rocha, MD, PhD; Shashvat M. Desai, MD; Ashutosh P. Jadhav, MD, PhD; Tudor G. Jovin, MD

Core more than 70cc
Presentation within 6 hours
“FAST Progressors” 25%

Core less than 30cc; Presentation beyond 6 hours; “SLOW Progressors” 55%
Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct


| Functional independence at 90 days — no. (%) ¶ | 52 (49) | 13 (13) | 36 (24–47) | 33 (21–44) | >0.999 |

Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging


| Secondary efficacy outcome: functional independence at 90 days — no. (%) ¶ | 41 (45) | 15 (17) | 2.67 (1.60–4.48) | <0.001 |

NNT = 2.8
NNT = 3

Nogueira et al (NEJM, 2018); Albers et al (NEJM, 2018)
WHERE DO WE STAND CURRENTLY?

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
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</thead>
<tbody>
<tr>
<td>Patients should receive mechanical thrombectomy with a stent retriever if they</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>meet all the following criteria: (1) prestroke mRS score of 0 to 1; (2)</td>
<td></td>
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<tr>
<td>causative occlusion of the internal carotid artery or MCA segment 1 (M1); (3)</td>
<td></td>
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<tr>
<td>age ≥18 years; (4) NIHSS score of ≥6; (5) ASPECTS of ≥6; and (6) treatment can</td>
<td></td>
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<tr>
<td>be initiated (groin puncture) within 6 hours of symptom onset.</td>
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<table>
<thead>
<tr>
<th>Recommendations</th>
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<tr>
<td>In selected patients with AIS onset within 6-16 hours, anterior circulation</td>
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<tr>
<td>large vessel occlusion, and who meet other DAWN or DEFUSE 3 eligibility</td>
<td></td>
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<tr>
<td>criteria, mechanical thrombectomy is recommended.</td>
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</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
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</thead>
<tbody>
<tr>
<td>In selected patients with AIS within 6 to 24 hours of last known normal who</td>
<td>Ila</td>
<td>B-R</td>
</tr>
<tr>
<td>have LVO in the anterior circulation and meet other DAWN eligibility criteria,</td>
<td></td>
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<tr>
<td>mechanical thrombectomy is reasonable.</td>
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</table>

Guidelines for the Early Management of Patients with Acute Ischemic Stroke. A
guideline for healthcare professionals from the American Heart Association/American Stroke Association. Powers et al., Stroke 2018
RATES OF UTILIZATION – US AND WORLDWIDE

INDUSTRY ESTIMATES

Ev Treated Patients


US World wide

40%
110%

0 20000 40000 60000 80000 100000 120000 140000 160000
CURRENT STATE: CLINICAL AND PROCEDURAL RESULTS

<table>
<thead>
<tr>
<th></th>
<th>GWTG 1</th>
<th>STRATIS REGISTRY 2</th>
<th>TREVO REGISTRY 3</th>
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<tbody>
<tr>
<td>N</td>
<td>6756</td>
<td>984</td>
<td>2008</td>
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<tr>
<td>NIHSS (median)</td>
<td>17</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>% iv t-PA</td>
<td>68 %</td>
<td>64%</td>
<td>52%</td>
</tr>
<tr>
<td>% transferred</td>
<td>46%</td>
<td>45.2%</td>
<td>NR</td>
</tr>
<tr>
<td>Onset to puncture (min, median)</td>
<td>230</td>
<td>208</td>
<td>264</td>
</tr>
<tr>
<td>Door to puncture (min, median)</td>
<td>87</td>
<td>72</td>
<td>85</td>
</tr>
<tr>
<td>% reperfusion (mTICI 2b)</td>
<td>86%</td>
<td>88%</td>
<td>93%</td>
</tr>
<tr>
<td>Puncture to reperfusion (min, median)</td>
<td>NR</td>
<td>37</td>
<td>55</td>
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<tr>
<td>mRS 0-2</td>
<td>44.1%</td>
<td>56.5%</td>
<td>55.3%</td>
</tr>
<tr>
<td>sICH</td>
<td>6.7%</td>
<td>1.4%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Mortality</td>
<td>19.6%</td>
<td>14.4%</td>
<td>14%</td>
</tr>
</tbody>
</table>

1 Jahan et al., JAMA 2019, 2 Muller-Kronast et., Stroke 2017, 3 Binning et al., JAHA 2018
"There are known knowns. These are things we know that we know. There are known unknowns. That is to say, there are things that we know we don't know. But there are also unknown unknowns. There are things we don't know we don't know."

Donald Rumsfeld
CURRENT STATE OF KNOWLEDGE (0-6 hours)

Known knowns

• Highly effective in most patients with proximal LVO (t-PA and non t-PA)
• Rate of mRS 0-2 still not good enough
• Benefit is time dependent
• Benefit is present in all subpopulations included in studies (age, gender, NIHSS, occlusion location, baseline infarct size)
• No evidence that proof of mismatch is necessary
• No major safety concerns

Known unknowns

• Harm in subpopulations (eg largest infarcts)
• Benefit in populations not studied (distal occlusions, pre-existing disability, mild stroke severity, largest infarcts, BA occlusion)
• Procedural and peri-procedural aspects (stentrieviers vs aspiration, GA vs awake, BP, glucose management, adjunctive antithrombotics, primary stenting)
• Effect of advanced imaging helpful/neutral/harmful
• Need for iv thrombolysis (t-PA/TNK) at thrombectomy center
CURRENT STATE OF KNOWLEDGE (beyond 6 hours)

Known knowns

- Highly effective in patients (proximal LVO and mismatch defined by DAWN & DEFUSE 3 criteria)
- Benefit is less strongly associated with time to treatment
- Benefit is not associated with mode of presentation (wake-up vs witnessed vs unwitnessed)
- No major safety concerns

Known unknowns

- Benefit in populations not meeting DAWN/DEFUSE criteria (distal occlusions, pre-existing disability, mild stroke severity, larger infarcts, less or no mismatch, beyond 24 hours)
- Optimal imaging modality for mismatch (clinical vs perfusion, core by CT only vs CTP vs MRI)
- Harm in subpopulations (eg largest infarcts)
- Procedural and peri-procedural aspects
- Role of iv thrombolysis
HOW CAN WE IMPROVE ??

SYSTEMS OF CARE - CRUCIAL TIME POINTS FOR IAT

- First Medical Contact
- ED Arrival
- Imaging ± iv thrombolysis
- Groin Puncture
- Reperfusion

Direct to thrombectomy center
Inter-facility transfers
WEARABLES - THE FUTURE OF STROKE DETECTION?

Samsung Designs Wearable Stroke-Detecting Device

By Suzanne Hodsden

Samsung has developed a prototype of a wearable device that can track brainwaves and alert the user of the very earliest signs of an impending stroke. The device is designed to be compatible with mobile devices and is capable of analyzing a number of neurological health markers.

Samsung is calling the early prototype of the device the Early Detection Sensor & Algorithm Package (EDSAP), and the project has been in development for the past two years, reports CNET Magazine.
TRIAGE DECISIONS SHOULD BE MADE IN THE FIELD

Remote assessment
Geo-location
Expert Stroke Neurologist
Transfer decision
Stroke
LVO DETECTION CLINICAL SCALES ± DEVICES
Comprehensive Stroke Center
Transfer option A
Primary Stroke Center
Transfer option B
RACECAT
Transfer to the Local Stroke Center versus Direct Transfer to Endovascular Center of Acute Stroke Patients with Suspected Large Vessel Occlusion in the Catalan Territory (RACECAT): Study protocol of a cluster randomized within a cohort trial

Exclusion:
- Areas covered by an EVT-SC

EMS identification
- Acute Stroke Patients
- RACE >3
- <8h from onset or unknown
- Age ≤85

Contact with Telestroke neurologist
- Real-time Video and Geolocalization

Eligibility Criteria:
- RACE >4
- Estimated arrival at a EVT-SC <7h from onset
- pre-morbid mRS 0-2

Website RANDOMIZATION 1:1
According to a predefined temporal (hours/day) sequence

Group 1
LOCAL STROKE CENTER (Loc-SC)

Group 2
ENDOVASCULAR CENTER (EVT-SC)

Unstable clinical status

Abilleira et al (IJS, 2019)
AI APPLICATIONS FOR LVO STROKE

New Devices and Techniques

RAPID
Non-contrast CT viewer.
Automated ASPECTS identification.
Non-dynamic PDF.

Brainomix®
Non-contrast CT viewer.
Automated ASPECTS & hypodense volume measurement.
Dynamic image viewing.

iz.ai
Non-contrast CT viewer.
No automated ASPECTS, rather, simplified CTA and CTP direct LVO characterization workflow.
Dynamic image viewing.

CT Perfusion Scan

Osia Sphere perfusion maps automatically emailed or pushed to mobile device.
Non-dynamic PDF and Dynamic images.

CT Angiography Scan

RAPID automatically quantifies collateral blood vessel density.
Indirect LVO detection.
e-CTA automatically quantifies both collateral blood flow density and the LVO directly.
Direct LVO detection using AI.

Immediate AI-mediated Activation of Emergency Stroke Treatment Systems

None, user interprets the imaging in context of thrombectomy criteria.

Yes, AI independent thrombectomy activation.
Secure, HIPAA-compliant text messaging and calling platform for the coordination care.

Figure 5  Software comparison acute stroke diagnostic and triage-capable software that incorporate artificial intelligence (AI) for acute stroke imaging and emergency treatment system activation. ASPECTS, Alberta Stroke Program Early CT Score; CTA, CT angiography; CTP, CT perfusion; HIPAA, Health Insurance Portability and Accountability Act; LVO, large vessel occlusion; PACS, picture archiving and communication system.
Direct transfer to angiosuite to reduce door-to-puncture time in thrombectomy for acute stroke

- Direct to angio vs Direct to CT: 42 min faster door to groin
- Direct to angio vs Direct to ED: 76 min faster door to groin

Ribo et al (JNS, 2017)
Reversible model of MCA occlusion did not exist before effective thrombectomy became available!
Prehospital Use of Magnesium Sulfate as Neuroprotection in Acute Stroke

Jeffrey L. Saver, M.D., Sidney Starkman, M.D., Marc Eckstein, M.D., Samuel J. Stratton, M.D., Franklin D. Pratt, M.D., M.P.H.T.M., Scott Hamilton, Ph.D., Robin Conwit, M.D., David S. Liebeskind, M.D., Gene Sung, M.D., Ian Kramer, M.D., Gary Moreau, M.D., Robert Goldweber, M.D., and Nerses Sanossian, M.D., for the FAST-MAG Investigators and Coordinators*

FRONTIER trial (NCT02315443) – Ultra-Early use
First modeled in primates

Then repeated in people

Onset 911 Suspected stroke NA-1 Dosing Standard care Neuro Eval (90d)

Median interval from onset to dosing in first 300 patients is 59 minutes

Saver et al (NEJM, 2015); Courtesy of Michael Tymianski
ESCAPE NA-1 Global Pivotal Trial
Topline Data Arriving Q4 2019

- 50 Sites
- 1,105 patients
- Passed Interim Analysis
- Primary endpoint acceptable by FDA for registration
- Largest ongoing global stroke trial

STAY TUNED – TOMORROW 2/20 11:00 AM
UPMC Stroke Institute

Ashutosh P. Jadhav
Brain Jankowitz
Lori Massaro
Ben Morrow
Lawrence R. Wechsler
Maxim Hammer
Vivek Reddy
Matthew Starr
Marcello Rocha
Michael Horowitz
Viktoria Totoraitis
Dan Victor Giurgiutiu
Amin Aghaebrahim
Cynthia Kenmuir
Brain Jankowitz
Andrew Ducruet
Yvonne Cannon

Cooper Neurological Institute

David Campbell
Deepak Gulati
Chris Streib
Srikant Rangaraju
Sunanda Nanduri
Hazem Shoirah
Al Al-Bayati
Anat Horev
Phil Parry
Paul Richard
Ramesh Grandhi
Guillermo Linares
Mohammad Juuma
Syed Zaidi
Lisa Baxendell
Sharon DeCesare

Brain Jankowitz
Terri Yeager
Ainsley Smith
Ryna Then
James Siegler
Jesse Thon
Hamza Shaikh
Tappan Kavi
Nitin Puri
Warren Goldman
Katherine Ginty
Drew Nice