Update
2019 International Stroke Conference

Michael Frankel, MD
Director of the Marcus Neuroscience and Stroke Center & Marcus Stroke Network
Chief of Neurology
Grady Memorial Hospital
Lead Neurologist, GA Coverdell Acute Stroke Registry
Professor & Director of Vascular Neurology
Emory University School of Medicine
Disclosures

- Research support
  - Nico Corporation (ENRICH trial)
## Table. Good Outcome With Endovascular Therapy or Control Under General Anesthetic vs Conscious Sedation

<table>
<thead>
<tr>
<th>Type of Anesthesia</th>
<th>Endovascular Therapy (%)</th>
<th>Control (%)</th>
<th>Relative Risk (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General anesthesia (n = 26)</td>
<td>23</td>
<td>17</td>
<td>1.4 (0.6 - 3.2)</td>
</tr>
<tr>
<td>Conscious sedation (n = 66)</td>
<td>53</td>
<td>17</td>
<td>3.2 (1.9 - 5.3)</td>
</tr>
</tbody>
</table>

*aGood outcome was defined as a modified Rankin Scale score of 0 to 2.*
Deferoxamine mesylate (DFO)

Background:
Binds iron

- Small trial called "hi-DEF" 42 pts 2014. 62 mg/kg/d x 5 days (ARDS)
- i-Def -- Intracerebral Hemorrhage Deferoxamine trial
- 294 patients within 24 hours of ICH onset
- NIHSS > 6
- GCS 6
- DFO infusion at a lower dose of 32 mg/kg per day or placebo for 3 days
- Median clot size = 13 cc
- Excluded aspiration, pneumonia, or evident bilateral pulmonary infiltrates

90-day follow-up (primary endpoint)
- 34.3% of DFO vs 32.9% of placebo mRS 0-2 (ns)

180-day follow-up (secondary endpoint)
- Adj risk diff = 15.6%,
- The adjusted odds of achieving a good outcome were 26% higher at 180 days (aOR, 1.26; 95% CI, 0.82 - 1.93).
- No increase in serious adverse events (27.1% vs 33.3%), 90-day mortality (6.9% vs 7.5%), or pulmonary complications, including ARDS (1.4% vs 0.7%).
- Next steps – possibly Phase III trial proposal with 180 day outcome measurement as primary endpoint
Main results - BP intensity arm
ISC Hawaii - 7 February 2019

Craig Anderson MD PhD
Tom Robinson MD

For the ENCHANTED Investigators/coordinators, 110 hospitals, 15 countries
In the international, open-label Enhanced Control of Hypertension and Thrombolysis Stroke
• 2227 patients (74% recruited in Asia)
• randomly assigned to one of two BP management groups within 6 hours of stroke onset.

• Alteplase-eligible patients
• 62% men; 73.7% Asian; mean age, 66.9 years
• 110 hospitals in 15 countries
• March 2012 to April 2018
• mild to moderate severity (NIH > 7)
• Active arm: SBP goal was less than 130 to 140 mmHg within an hour; SBP was then sustained for up to 72 hours using locally available agents.
• Standard management group targeted SBP was less than 180 mmHg over 72 hours.
• Median time from onset to randomization was 3.3 hrs.
• Mean SBP over 24 hours was 144.3 mmHg for the intensive group vs 149.8 mmHG for the standard group.
• Although this resulted in a statistically significant difference (P < .0001), it did not reach the planned 15 mmHg difference.
• There was no significant between-group difference in improved mRS scores (odds ratio [OR], 1.01; 95% confidence interval [CI], 0.87 – 1.17; P = .87).
• There was no significant heterogeneity in the primary endpoint with respect to age, ethnicity, baseline systolic blood pressure, ischemic stroke subtype, and dose,
• Fewer cases of any ICH in the intensive group (OR, 0.75; 95% CI, 0.60 – 0.94; P = .014).
• Fewer reports of ICH as a serious adverse event, including major ICH, in the intensive group (5.5% vs 9.0%; OR, 0.59; P = .002).
• Intensive BP lowering "was not shown to be superior to guideline-recommended BP lowering for primary disability outcome, and there was a consistency of neutral findings in all prespecified subgroups

This finding might be related to the smaller than planned difference in blood pressure between the groups, or the inclusion of mainly patients with mild-to-moderate stroke.
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intensive N=1081</th>
<th>Guideline N=1115</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age median (iqr)</td>
<td>67 (59-75)</td>
<td>67 (59-76)</td>
</tr>
<tr>
<td>Female</td>
<td>37%</td>
<td>39%</td>
</tr>
<tr>
<td>China (origin)</td>
<td>65%</td>
<td>65%</td>
</tr>
<tr>
<td>Asian (ethnicity)</td>
<td>74%</td>
<td>74%</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>72%</td>
<td>71%</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td>165/91</td>
<td>165/91</td>
</tr>
<tr>
<td>NIHSS median (iqr) score</td>
<td>7 (4-12)</td>
<td>8 (4-12)</td>
</tr>
<tr>
<td>Aspirin / other APT</td>
<td>16%</td>
<td>19%</td>
</tr>
<tr>
<td>Large artery atheroma</td>
<td>43%</td>
<td>45%</td>
</tr>
<tr>
<td>Cardio-embolism</td>
<td>13%</td>
<td>14%</td>
</tr>
<tr>
<td>Small vessel disease</td>
<td>31%</td>
<td>27%</td>
</tr>
</tbody>
</table>
ENCHANTED BP Changes
Mean SBP difference of 6 mmHg in 24 hrs
<table>
<thead>
<tr>
<th>Event Description</th>
<th>Intensive blood pressure lowering group</th>
<th>Guideline-recommended blood pressure lowering group</th>
<th>Treatment effect</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any intracranial haemorrhage*</td>
<td>160/1081 (14.8%)</td>
<td>209/1115 (18.7%)</td>
<td>0.75 (0.60–0.94)</td>
<td>0.0137</td>
</tr>
<tr>
<td>Any intracranial haemorrhage reported as a serious adverse event</td>
<td>59/1081 (5.5%)</td>
<td>100/1115 (9.0%)</td>
<td>0.59 (0.42–0.82)</td>
<td>0.0017</td>
</tr>
<tr>
<td>Major intracerebral haemorrhage based on central adjudication of brain imaging</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic intracerebral haemorrhage, SITS-MOST criteria*</td>
<td>14/1081 (1.3%)</td>
<td>22/1115 (2.0%)</td>
<td>0.65 (0.33–1.28)</td>
<td>0.2143</td>
</tr>
<tr>
<td>Symptomatic intracerebral haemorrhage, NINDS criteria†</td>
<td>70/1081 (6.5%)</td>
<td>84/1115 (7.5%)</td>
<td>0.85 (0.61–1.18)</td>
<td>0.3321</td>
</tr>
<tr>
<td>Symptomatic intracerebral haemorrhage, ECASS2 criteria§</td>
<td>46/1081 (4.3%)</td>
<td>57/1115 (5.1%)</td>
<td>0.82 (0.55–1.23)</td>
<td>0.3431</td>
</tr>
<tr>
<td>Symptomatic intracerebral haemorrhage, ECASS3 criteria¶</td>
<td>21/1081 (1.9%)</td>
<td>30/1115 (2.7%)</td>
<td>0.72 (0.41–1.26)</td>
<td>0.2467</td>
</tr>
<tr>
<td>Symptomatic intracerebral haemorrhage, IST-3 criteria</td>
<td>24/1081 (2.2%)</td>
<td>37/1115 (3.3%)</td>
<td>0.66 (0.39–1.11)</td>
<td>0.1198</td>
</tr>
<tr>
<td>Large parenchymal intracerebral haemorrhage‖</td>
<td>56/1081 (5.2%)</td>
<td>80/1115 (7.2%)</td>
<td>0.71 (0.50–1.01)</td>
<td>0.0535</td>
</tr>
<tr>
<td>Any intracerebral haemorrhage on brain imaging within 7 days</td>
<td>143/1081 (13.2%)</td>
<td>180/1115 (16.1%)</td>
<td>0.79 (0.62–1.00)</td>
<td>0.0542</td>
</tr>
<tr>
<td>Fatal intracerebral haemorrhage within 7 days</td>
<td>5/1081 (0.5%)</td>
<td>14/1115 (1.3%)</td>
<td>0.37 (0.13–1.02)</td>
<td>0.0541</td>
</tr>
</tbody>
</table>
Primary Efficacy Outcome by pre-specified Subgroups

No Significant heterogeneity in the primary efficacy endpoint.
In lysis-eligible patients with acute ischemic stroke, more intensive BP lowering (<140mmHg target):

- *Not shown to be superior* to guideline-recommended BP lowering (<180mmHg) for primary disability outcome
- *Consistency* of neutral findings in all pre-specified subgroups
- *Shown to be safe* with respect to mRS scores and SAEs
- *Evidence* for lower risk of intracranial hemorrhage (including intracerebral hemorrhage)
Clinical implications

Role of more intensive BP lowering than recommended in guidelines (systolic <180mmHg) in lysis-eligible AIS patients?

- No evidence to support a major change in the guidelines
- Treatment – safe, potential to reduce serious brain haemorrhage

Further research - brain imaging database analyses to understand why reduction in risk of ICH did not translate into improved recovery.
Transfer patients had longer median times from last known well to study site arrival (9.43 vs 9 hours) and more favorable collateral profiles (based on hypoperfusion intensity ratio): median for transfer, 0.35 (IQR, 0.18-0.47) vs 0.42 (IQR, 0.25-0.56) for direct (P = .05). The overall functional independence rate (90-day modified Rankin Scale score 0-2) in the thrombectomy group did not differ (direct 44% vs transfer 45%) nor did the treatment effect (direct OR, 2.0; 95% CI, 0.9-4.4 vs transfer OR, 3.1; 95% CI, 1.6-6.1).

**CONCLUSIONS AND RELEVANCE** In late-window patients selected by penumbral mismatch criteria, both the favorable outcome rate and treatment effect did not decline in transfer patients. These results have health care implications indicating transferring potential candidates for late-window thrombectomy is associated with substantial clinical benefits and should be encouraged.
• In the 6 hour trials, transferred pts appeared to do worse than those taken directly to thrombectomy hospitals
• Early-window patients tend to be selected on time alone (e.g. w/in 6 hours)
• Late-window patients are selected by imaging — they are known to have salvageable brain tissue so the treatment delay may not matter
Evaluating Image-Guided, Minimally Invasive Surgery for ICH: MISTIE III Results

Daniel F. Hanley, MD
Mario Zuccarello, MD
Issam A. Awad, MD

Principal Investigators
On behalf of the MISTIE investigators, patients and families
• 78 hospitals in the United States, Canada, Europe, Australia, and Asia
• 506 patients with an ICH of at least 30 mL
• Glasgow Coma Scale score of ≤ 14
• NIHSS ≥ 6
• Pre-stroke mRS score of ≤ 1
• Patients were randomly assigned to receive standard treatment — typically intense blood pressure control, artificial ventilation, swelling management, and watchful waiting — or the MISTIE procedure after the hematoma had stabilized but within 72 hours.

The surgery involved drilling a dime-sized hole in the skull, performing image-guided aspiration with a rigid cannula, and then placing a soft drainage catheter in the epicenter of the hematoma. Alteplase (1.0 mg in 1 mL every 8 hours) was then delivered to the clot with the soft catheter until less than 15 mL ICH was reached or 9 doses of alteplase were given.
1 year good outcome (mRS 0-3): 45% vs 41% (P = .33).
Exploratory analyses...
Good functional recovery was 10.5% greater in the 58% of patients with < 15 mL of residual clot volume (P = .03).

ICH removal of more than 70% was independently associated with twice the likelihood of good functional outcome in multivariable analyses (odds ratio, 2.05; P = .025).

Bottom line
• Minimally invasive catheter evacuation followed by thrombolysis did not improve outcome after a large intracranial hemorrhage (ICH)
• Functional recovery was better when more complete clot removal was achieved
• Acute ischemic stroke
• Type 2 diabetes and glucose > 110
• Known diabetes and glucose of > 150
• NIHSSS 3 - 22

• 1100 hyperglycemic patients
• 12 hours of stroke symptom onset

• Intensive IV treatment (n = 581; 55% men; 63% white, 31% black; mean age, 66 years)
• Standard subcutaneous treatment (n = 570; 54% men; 65% white, 27% black; mean age, 66 years).

Primary Efficacy Outcome: mRS
Primary safety outcome: severe hypoglycemia < 40

The median time to treatment randomization was 7.1 hours for both groups.

SHINE Stroke Hyperglycemia
Insulin Network Effort

Karen C. Johnston, UVA
SHINE Trial Sites

- 70 participating sites
- 63 sites enrolled
- 1151 total patients enrolled (4/12 – 8/18)

Top Enrolling Sites
1. NYP/Columbia
2. Emory/Grady
3. Ohio State

- SHINE Enrolling Site
- NETT/Siren CCC - UM
- NETT/Siren SDMC - MUSC
Blood Glucose Separation

Intensive target: 80-130 mg/dL
Standard target: 80-179 mg/dL

Overall Mean
179 mg/dL
118 mg/dL
• Primary (Good outcome)
  • 20.5% of those receiving intensive therapy
  • 21.6% of those receiving standard therapy
  • After adjusting for baseline stroke severity and use of thrombolysis, the adjusted relative risk was 0.97 (0.87 – 1.08; P = .55).

• Secondary (Good outcome)
  • NIHSSS 0,1 at 90 days: 43.7% vs 44.7% (RR, 0.98)
  • Barthel Index 95 to 100: 55.2% vs 54.7% (RR, 1.01)

Severe hypoglycemia occurred in 15 members of the intensive treatment group and zero members of the standard treatment group (risk difference, 2.58; 95% CI, 1.29 – 3.87).
BHF Glyceryl trinitrate for pre-hospital ultra-acute stroke: Main results from the Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial-2 (RIGHT-2)

Philip M Bath
Stroke Association Professor of Stroke Medicine
On behalf of RIGHT-2 Investigators
• GTN patch (5 mg as Transderm-Nitro 5) or a sham patch containing DuoDERM hydrocolloid dressing
• 516 paramedics from eight ambulance services in the United Kingdom
• 850 patients with (FAST) score of 2 or 3
• SBP > 120

• 1149 patients were enrolled
• median time to randomization was 71 minutes.
• Ischemic stroke or transient ischemic attack (TIA)
• Primary outcome — mRS score at 90 days
• No difference (mRS of 3 for both groups)

"GTN in mimics was positive, so we have a new treatment for stroke mimics," Bath said to a round of laughter. "And please don't ask me to explain that because I haven't a clue."

A suggestion of harm with very early GTN in patients with intracerebral hemorrhage, very early stroke (less than 1 hour), and severe stroke; and a positive effect in stroke mimics.

Phillip Bath - UK
mRS by subgroups: in Stroke/TIA

One interaction:
▲ Time: GTN worse when given very early

Time to randomisation
<1 h 179/420 162/408
1-2 h 148/420 161/408
>2 h 93/420 85/408

No interactions:
▲ Age
▲ Sex
▲ Pre-morbid mRS
▲ HT
▲ Previous stroke
▲ Previous nitrate
▲ GCS
▲ FAST
▲ SBP
▲ AF
▲ Diagnosis

RIGHT-2 Investigators. Lancet 2019; in press
FDA: non-significant risk device study
At-home rehab comparable to clinic-based therapy to improve mobility

- Randomized, assessor-blinded, non-inferiority trial
- N = 124 stroke survivors
- Average age 61
- 11 U.S. StrokeNet Clinical Trial Network sites
- 6 weeks of intensive rehabilitation therapy targeting arm weakness
- Randomized to receive therapy either in the clinic using traditional methods or in their home using a telerehabilitation system.

- A computer-based telerehabilitation system
- Delivered to patient’s home uses “game-ified” therapy activities
- Exercises and educational sessions (such as “Stroke Jeopardy”)
- Therapists can assess progress via videoconference
- Clinic-based therapy: drive to the clinic and perform standard exercises and therapeutic activities with a therapist without a computer and without game-ification of these activities,
In-Clinic Group

- **18 supervised treatment sessions** (70 minutes)
  -- At the research center, with a therapist
- **18 unsupervised treatment sessions** (70 minutes)
  -- In the home, using an individualized booklet

Telerehabilitation

- Study team delivered a telerehabilitation system to the home
- **18 supervised treatment sessions** (70 minutes)
  -- In the home, 30 min therapist videoconference at start
- **18 unsupervised treatment sessions** (70 minutes)
  -- In the home, using telerehab system (no therapist contact)

Games could be adjusted in relation to motor control, e.g., movement speed, timing, planning, range of motion, target size, cognitive demand, hemifield bias, bimanual, sustained, proximal vs. distal, and 1st person vs. 3rd person perspective
Telerehabilitation

Transfer Object

Grasp and hold object with one hand. Transfer object to other hand. Reverse. Use objects of different shapes, sizes, and weight.

In the past week of arm rehab therapy you have been doing as part of the research study. How satisfied are you with the therapy?

I find the tasks challenging.

Score: 5
Time: 125

Current total: 12. Press 1 to hit or 1 to stay.
Results

The non-inferiority margin (2.47 points) fell outside of the 95% CI for 0.06 points (adjusted* group difference in ΔFM)

Telerehabilitation is non-inferior.

Compliance was high and similar between both groups. Arm function improved substantially and equivalently in both groups.

*Adjusted for age, baseline FM, time post-stroke, enrollment site, and stroke subtype
Outcomes After Endovascular Stroke Therapy in High Versus Low Volume Centers


Assistant Professor
Department of Neurology
UT Health McGovern School of Medicine
Houston, Texas
Methods

Study Design: Retrospective cross-sectional study, using HCUP State Inpatient Database (SID) and State Emergency Department Database (SEDD) on all discharges from nonfederal acute care hospitals in Florida from 2006 - 2016. And Nationwide Inpatient Sample from 2012 - 2016.

Methods:
Patients were identified using ICD-9 and ICD-10 diagnosis and procedure codes. Ischemic stroke was defined using previously validated codes. EST was defined as procedure code 39.74 or 03CG3ZZ and a corresponding code for ischemic stroke. IV tPA treatment was defined as procedure code 99.10 or 3E03317 and a corresponding code for ischemic stroke.

Patients in the FL cohort were identified in SID and then cross-referenced in SEDD to identify any patients that received IV tPA at a different hospital or were transferred from one hospital to another for EST.

Patients were excluded if they had any diagnosis or treatment of AVM, AV fistula, prior ICH or SAH or trauma.

Outcomes: Primary endpoint was discharge disposition.
These findings were maintained in the nation-wide cohort (OR, 1.3; 95% CI, 1.2-1.4). For AIS patients evaluated at EST-capable centers who were not treated with EST in the FL cohort, there was no effect on discharge outcomes by annual hospital EST volume (OR, 0.93; 95% CI, 0.83-1.1).
Conclusions

- In this large population-level study of patients treated with EST from 2006 - 2016, we observed a continuous increase in annual treatment rates and EST-performing hospitals.

- We observed a shift in procedural volume across a substantially greater number of hospitals.

- Patients treated with EST in hospitals with greater annual procedural volume had better discharge outcomes.
Cerebral Microbleeds and The Effect of Anticoagulation on Outcomes in 3699 Patients With Embolic Strokes of Undetermined Source: An Exploratory Analysis of The NAVIGATE ESUS Trial


on behalf of the NAVIGATE ESUS Investigators
• NAVIGATE ESUS
• 459 Centers
• 7,000 patients
• Rivaroxaban vs ASA
• Cerebral Microbleeds = higher risk of ischemic stroke AND ICH when > 3 CMB’s found

Discussion

• CMBs are prevalent in ESUS and associated with advancing age, East Asian ethnicity, hypertension, multi-territorial ESUS and chronic stroke (infarcts and occult ICH) on imaging.

• We observed greater rates of recurrent stroke, ischemic stroke, ICH and all-cause mortality in NAVIGATE ESUS participants with CMBs.

• In the first trial assessing interactions between CMBs and the effects of randomized anticoagulant therapy on clinical outcomes, treatment with rivaroxaban compared with aspirin was not associated with higher relative risk for ICH in persons with CMBs compared to those without CMBs.

• These results may be generalizable to other ischemic stroke subtypes.
• Goal: To find out if stroke risk differs by race during and after delivery
• Nationwide Inpatient Sample, 1998 to 2014.
• 68 million delivery hospitalizations
• 1.1 million post-delivery hospitalizations for women between 15- to 54-years-old
• 8241 women were diagnosed with stroke during delivery.
• 11,073 women were readmitted for stroke
• Black women vs White women
  • 64% higher risk for stroke during delivery
  • 66% higher risk for stroke during postpartum admissions
• Black and Hispanic women with preeclampsia
  • Twice as likely as white women to have a stroke during delivery
Things to be on the look out for…

- Current trials and those in planning stages
  - ESCAPE NA-1 – thrombectomy with or w/o neuroprotection (NA-1)
  - ARCADIA: Embolic stroke of uncertain source – apixaban vs ASA
  - SleepSmart - Screening for OSA – CPAP vs usual care
  - TIMELESS - IV Tenecteplase (TNK) vs placebo beyond 4.5 hours
  - MOST – Eptifibitide vs Argatroban vs Placebo after tPA
  - TRANSPORT 2 – TMS vs sham TMS to promote stroke recovery
  - ENRICH trial – minimally invasive clot evacuation vs med therapy
  - Thrombectomy for large core infarction

- New smartphone tools with AI to improve imaging evaluation

- Telerobotic thrombectomy