MARCUS STROKE & NEUROSCIENCE CENTER

Grady

Update
2019 International Stroke Conference

Michael Frankel, MD

Director of the Marcus Neuroscience and Stroke Center & Marcus Stroke Network

Chief of Neurology

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Disclosures

- Research support
  - Nico Corporation (ENRICH trial)

DEFUSE-3 Trial --- subgroup analysis

Table. Good Outcome With Endovascular Therapy or Control Under General Anesthetic vs Conscious Sedation[a]

Type of Anesthesia	Endovascular Therapy (%)	Control (%)	Relative Risk (95% Confidence Interval)
General anesthesia (n = 26)	23	17	1.4 (0.6 - 3.2)
Conscious sedation (n = 66)	53	17	3.2 (1.9 - 5.3)

[a]Good outcome was defined as a modified Rankin Scale score of 0 to 2.

Iron chelation therapy for ICH - iDef

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

Magdy Selim, MD, PhD, Beth Israel Deaconess Medical Center, Boston

Enchanted

Enhanced Control of Hypertension and Thrombolysis Stroke Study

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

Central project coordination

The George Institute for Global Health

Main funding

Australian Government National Health and Medical Research Council NHMRC

Stroke association

Other funding

National Council for Scientific and Technological Development of Brazil

Ministry for Health, Welfare and Family Affairs of the Republic of Korea

Takeda

ENCHANTED

- 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 $\geq$ 7)

Craig Anderson

National Health and Medical Research Council (NHMRC) of Australia and the UK Stroke Association.

- 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).

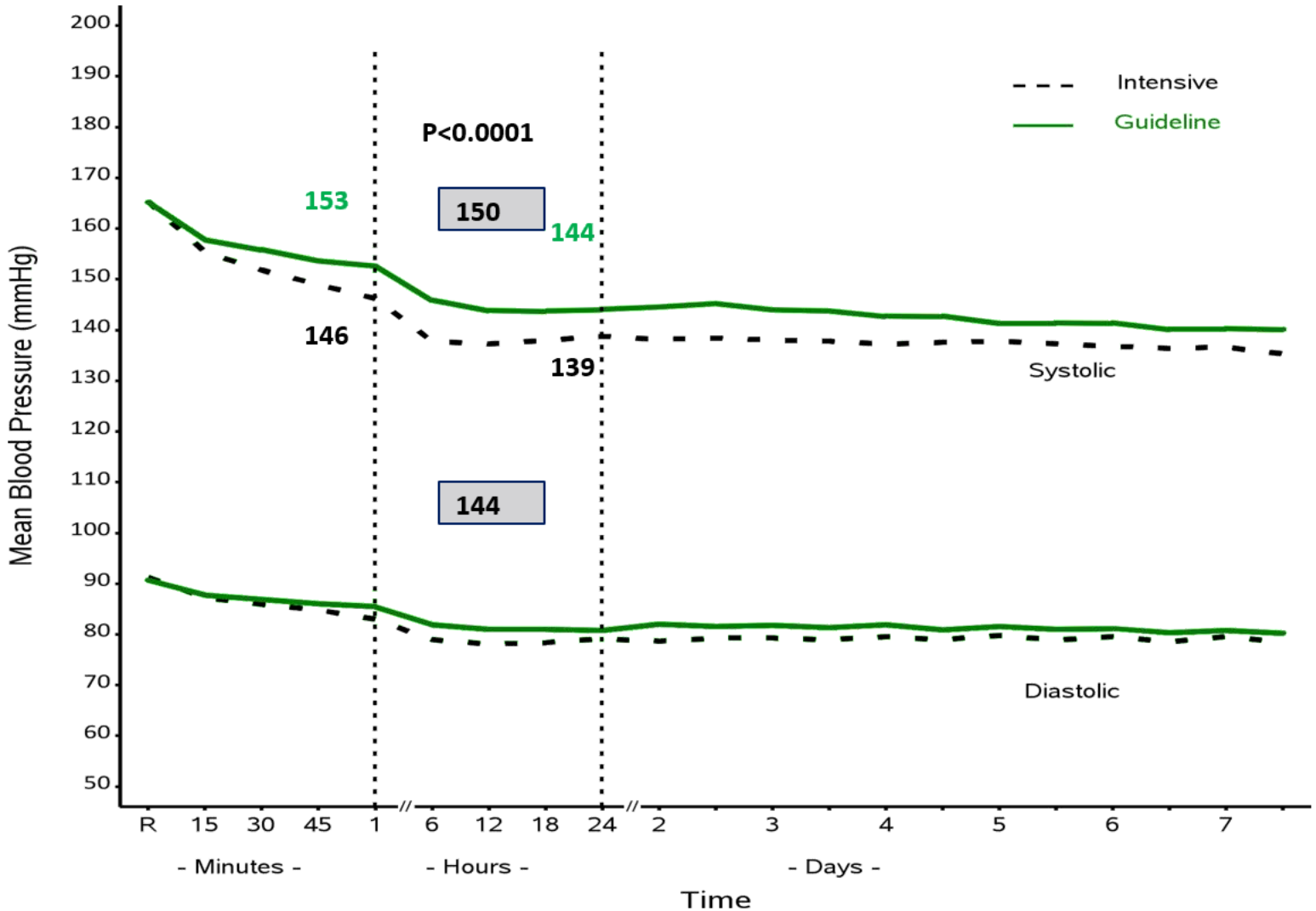
- Intensive BP lowering "was not shown to be superior to guideline-recommended BP lowering for primary disability outcome, and there was a consistency of neutral findings in all prespecified subgroups

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

Variable	Intensive N=1081	Guideline N=1115
Age median (iqr)	**67 (59-75)**	**67 (59-76)**
Female	37%	39%
China (origin)	**65%**	**65%**
Asian (ethnicity)	**74%**	**74%**
History of hypertension	72%	71%
Blood pressure (mmHg)	165/91	165/91
NIHSS median (iqr) score	**7 (4-12)**	**8 (4-12)**
Aspirin / other APT	16%	19%
Large artery atheroma	**43%**	**45%**
Cardio-embolism	13%	14%
Small vessel disease	**31%**	**27%**

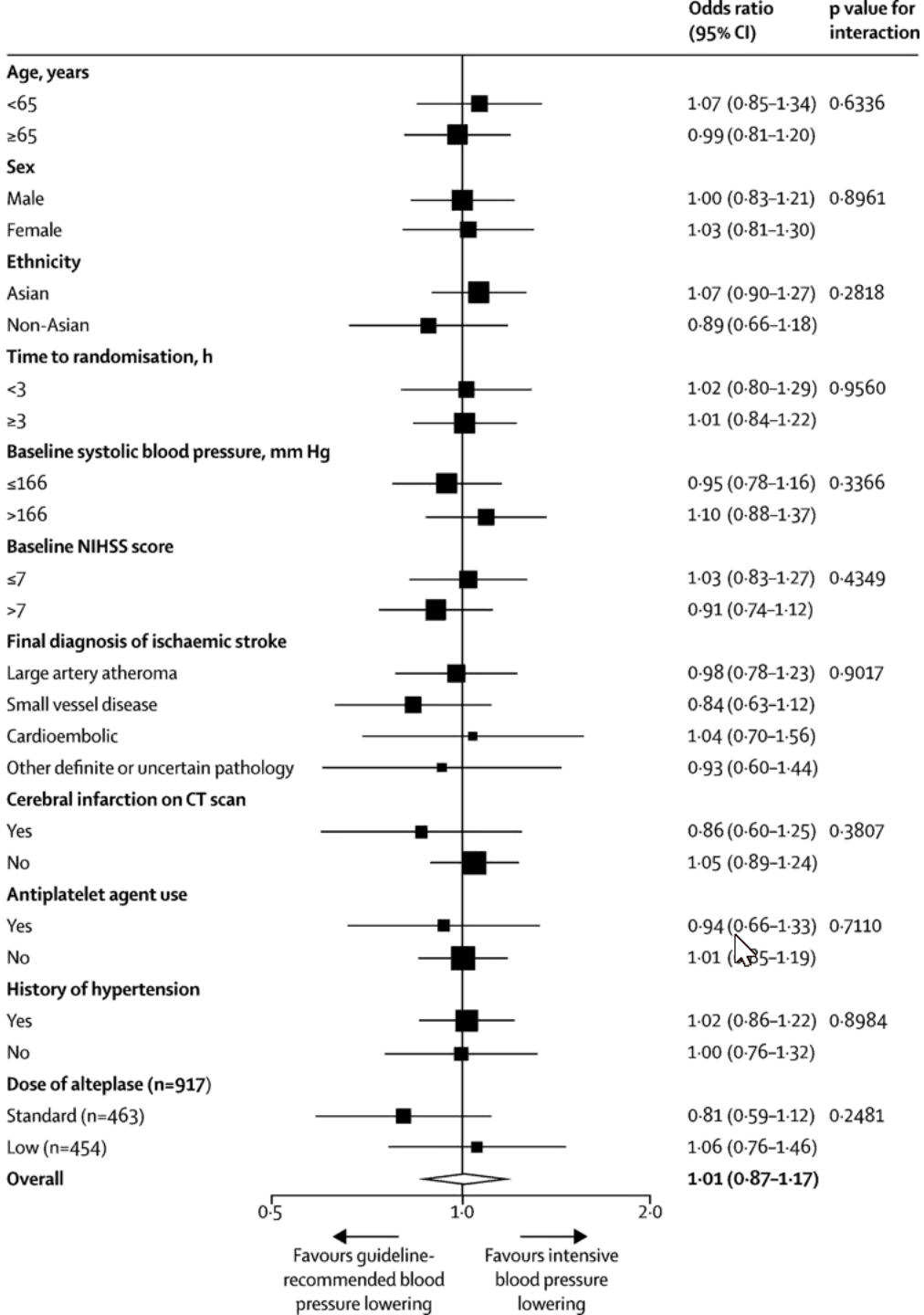
ENCHANTED BP Changes
Mean SBP difference of 6 mmHg in 24 hrs



	Intensive blood pressure lowering group	Guideline-recommended blood pressure lowering group	Treatment effect	p value
Any intracranial haemorrhage*	160/1081 (14·8%)	209/1115 (18·7%)	0·75 (0·60–0·94)	0·0137
Any intracranial haemorrhage reported as a serious adverse event	59/1081 (5·5%)	100/1115 (9·0%)	0·59 (0·42–0·82)	0·0017
Major intracerebral haemorrhage based on central adjudication of brain imaging				
Symptomatic intracerebral haemorrhage, SITS-MOST criteria†	14/1081 (1·3%)	22/1115 (2·0%)	0·65 (0·33–1·28)	0·2143
Symptomatic intracerebral haemorrhage, NINDS criteria‡	70/1081 (6·5%)	84/1115 (7·5%)	0·85 (0·61–1·18)	0·3321
Symptomatic intracerebral haemorrhage, ECASS2 criteria§	46/1081 (4·3%)	57/1115 (5·1%)	0·82 (0·55–1·23)	0·3431
Symptomatic intracerebral haemorrhage, ECASS3 criteria¶	21/1081 (1·9%)	30/1115 (2·7%)	0·72 (0·41–1·26)	0·2467
Symptomatic intracerebral haemorrhage, IST-3 criteria	24/1081 (2·2%)	37/1115 (3·3%)	0·66 (0·39–1·11)	0·1198
Large parenchymal intracerebral haemorrhage‖	56/1081 (5·2%)	80/1115 (7·2%)	0·71 (0·50–1·01)	0·0535
Any intracerebral haemorrhage on brain imaging within 7 days	143/1081 (13·2%)	180/1115 (16·1%)	0·79 (0·62–1·00)	0·0542
Fatal intracerebral haemorrhage within 7 days	5/1081 (0·5%)	14/1115 (1·3%)	0·37 (0·13–1·02)	0·0541

Primary Efficacy Outcome by pre-specified Subgroups

No Significant heterogeneity in the primary efficacy endpoint



ENCHANTED - major findings

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.

JAMA Neurology | Original Investigation

Outcomes of Thrombectomy in Transferred Patients With Ischemic Stroke in the Late Window
A Subanalysis From the DEFUSE 3 Trial

Amrou Sarraj, MD; Michael Mlynash, MD; Sean I. Savitz, MD; Jeremy J. Heit, MD, PhD; Maarten G. Lansberg, MD, PhD; Michael P. Marks, MD; Gregory W. Albers, MD

RESULTS Of the 296 patients who consented, 182 patients were randomized (66% were transfer patients and 34% directly presented to a study site). Median age was 71 years (interquartile range

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.

JAMA Neurol. doi:10.1001/jamaneurol.2019.0118
Published online February 7, 2019.

- 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

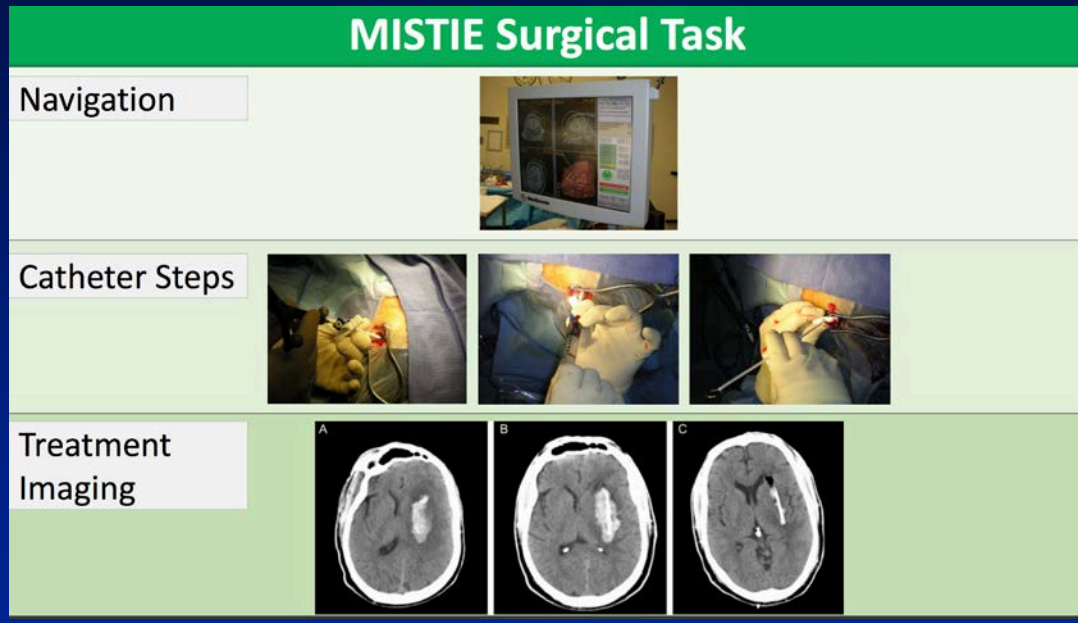
On behalf of the MISTIE investigators, patients and families

NIH National Institute of Neurological Disorders and Stroke
JOHNS HOPKINS MEDICINE
THE UNIVERSITY OF CHICAGO MEDICINE
UNIVERSITY OF Cincinnati
NIH StrokeNet PREVENTION | TREATMENT | RECOVERY

MISTIE - 3

- 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.

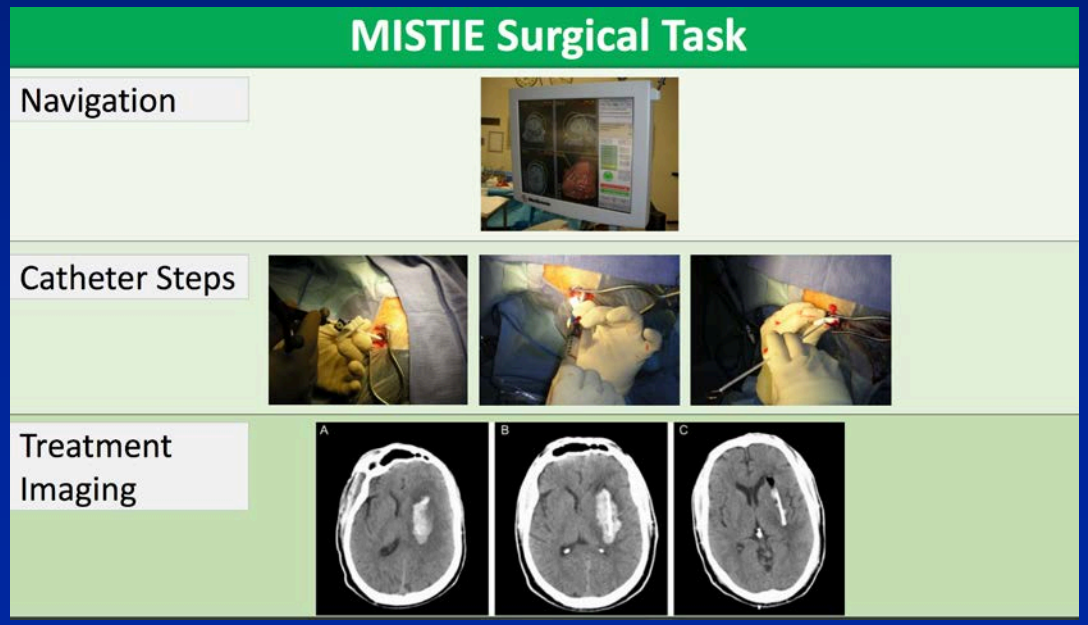


- Administration of alteplase (1mg in 1 mL every 8 hours) via the soft catheter, and passive hematoma clearance to < 15 mL or 9 doses of alteplase are given

MISTIE - 3

- 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

Daniel F. Hanley, Johns Hopkins University, Baltimore,

SHINE Stroke Hyperglycemia Insulin Network Effort

- 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).

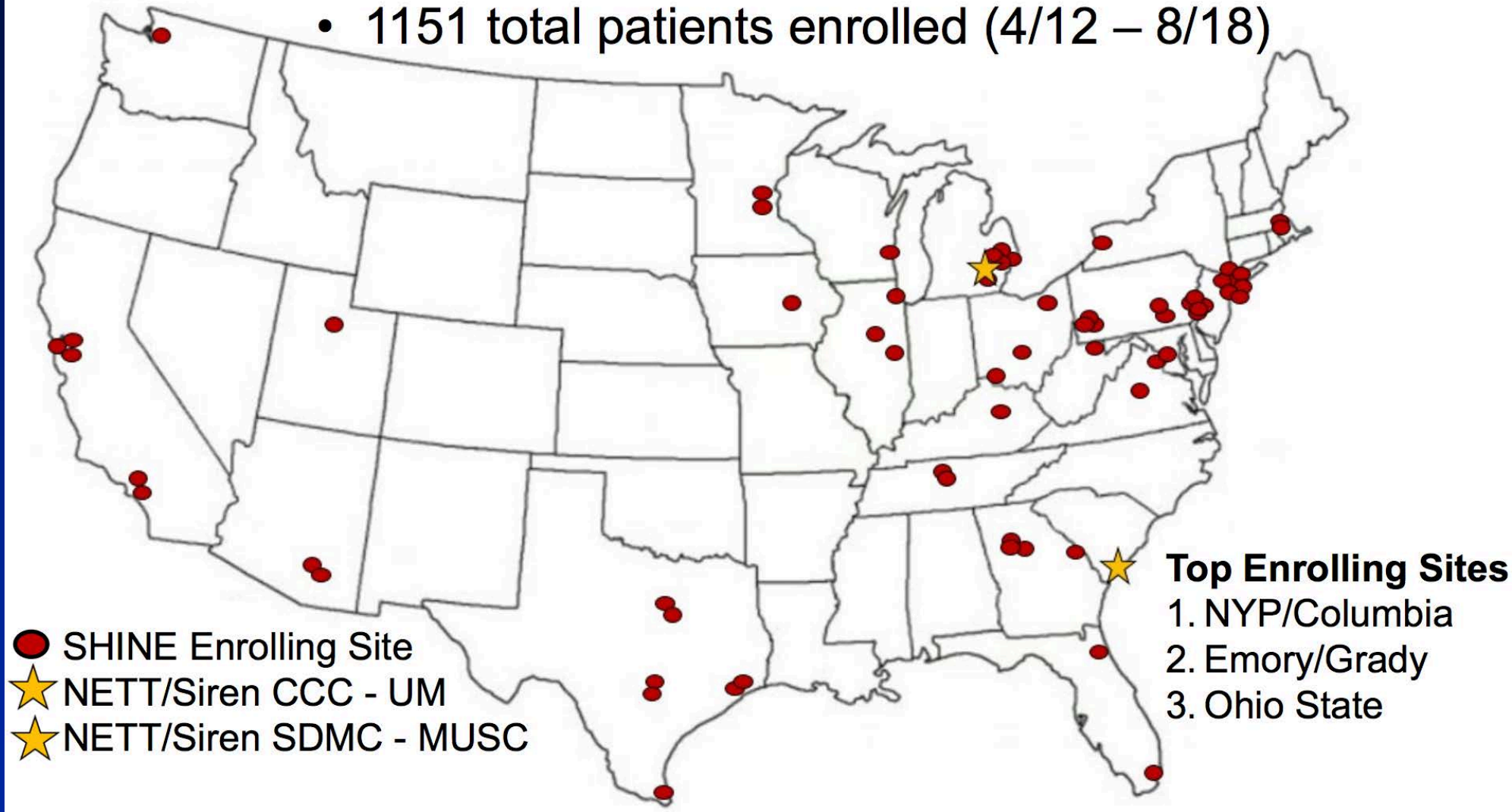
Primary Efficacy Outcome: mRS
Primary safety outcome: severe hypoglycemia < 40

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

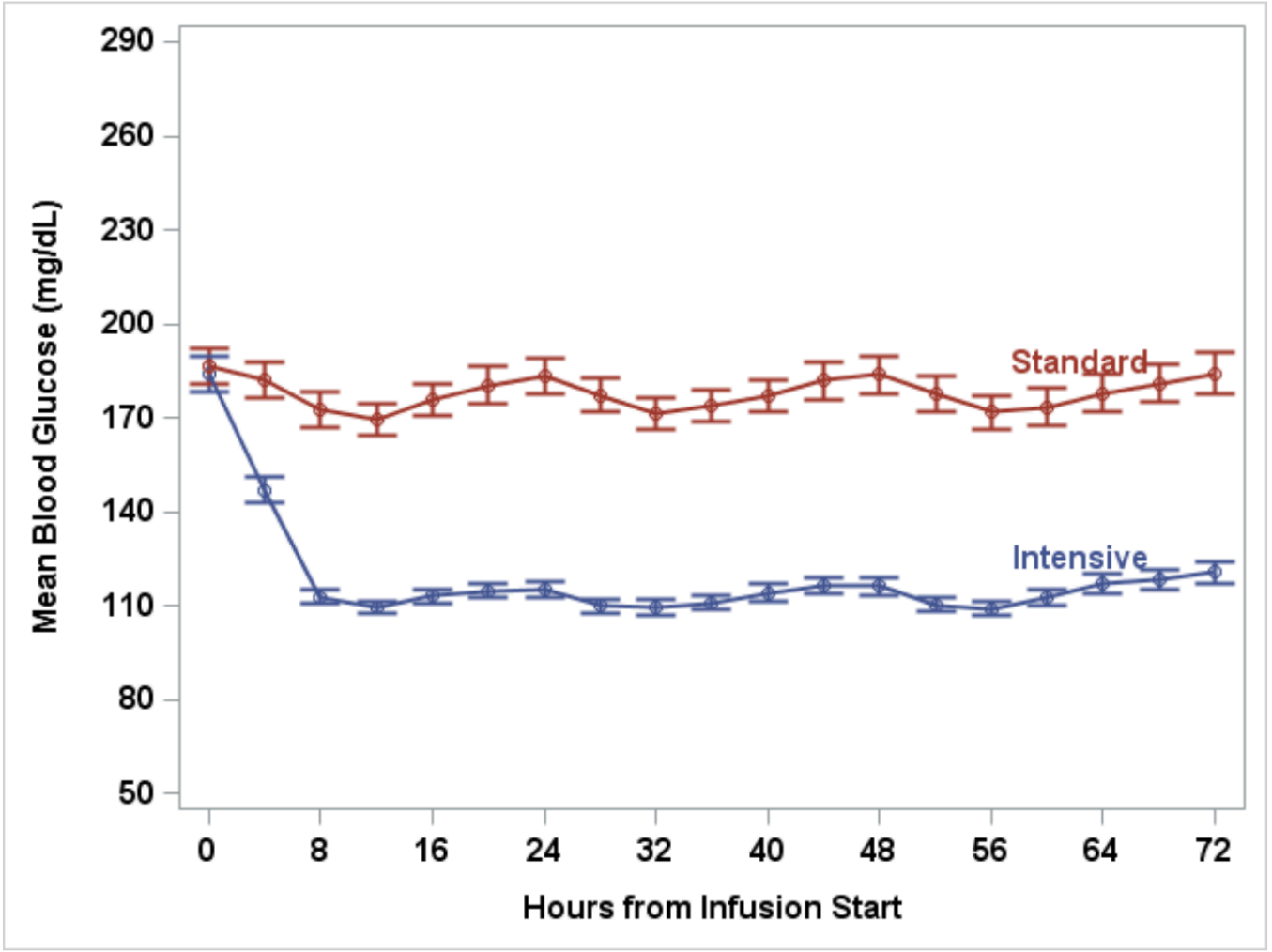
Karen C. Johnston, UVA

SHINE Trial Sites

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



Blood Glucose Separation



Overall Mean

179 mg/dL

118 mg/dL

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

SHINE Stroke Hyperglycemia Insulin Network Effort

- 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

Rapid Intervention With Glyceryl Trinitrate in Hypertensive Stroke Trial (RIGHT)-2 trial

- 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)

- Time of randomization was statistically significant (P = .014).
- Mortality at 90 days – no difference groups (23% vs 19%; aHR, 1.24; P = .17).
- In the ITT population, the adjusted common odds ratio (acOR) for the primary outcome was 1.04 (95% CI, 0.84 - 1.29; P = .69). Death rates were similar between 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."

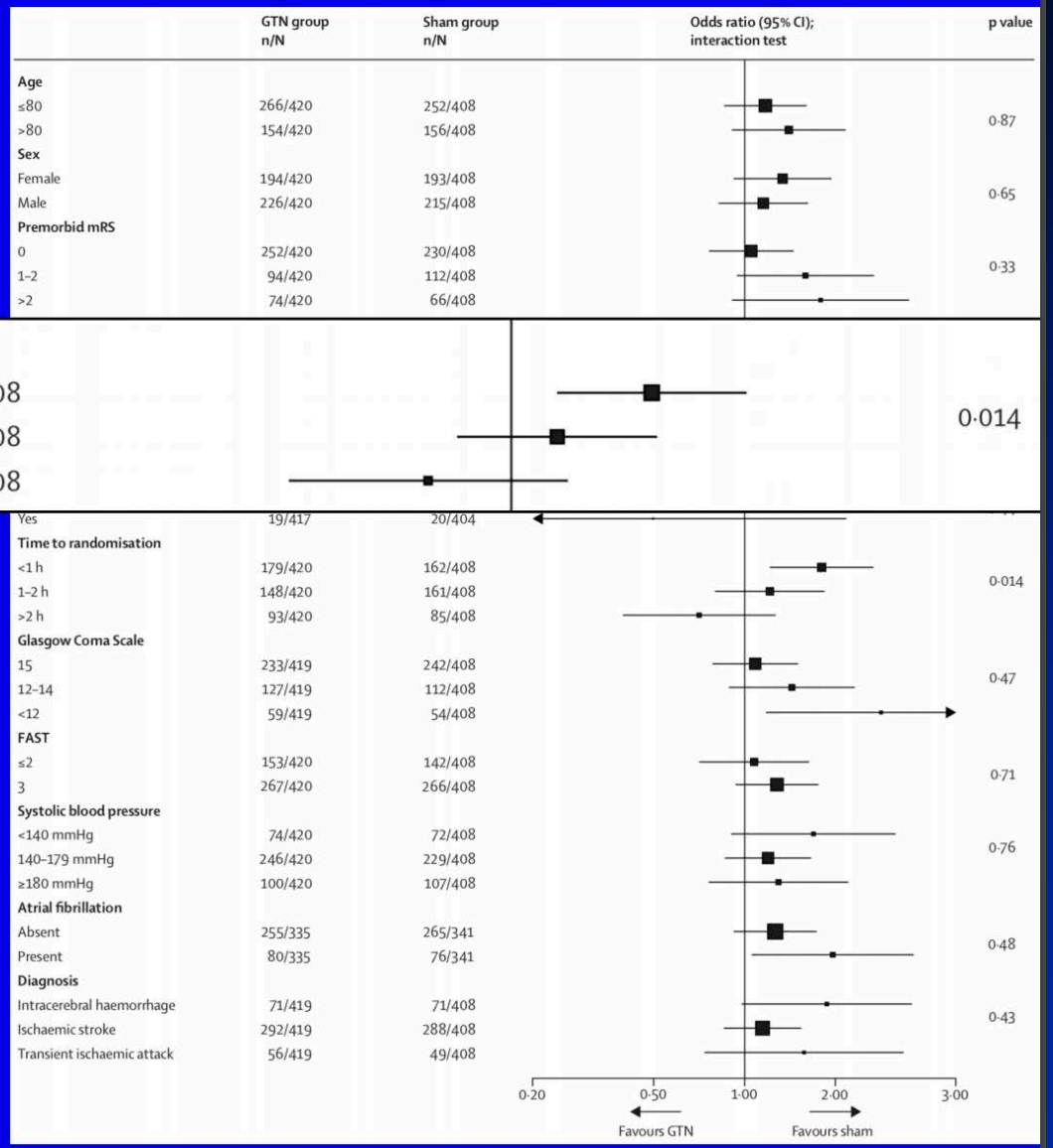
A suggestion of harm with very early GTN in patients with intracerebral hemorrhage, very early stroke (less than 1 hour), and severe stroke; and a positive effect in stroke mimics.

Phillip Bath - UK

mRS by subgroups: in Stroke/TIA

One interaction:

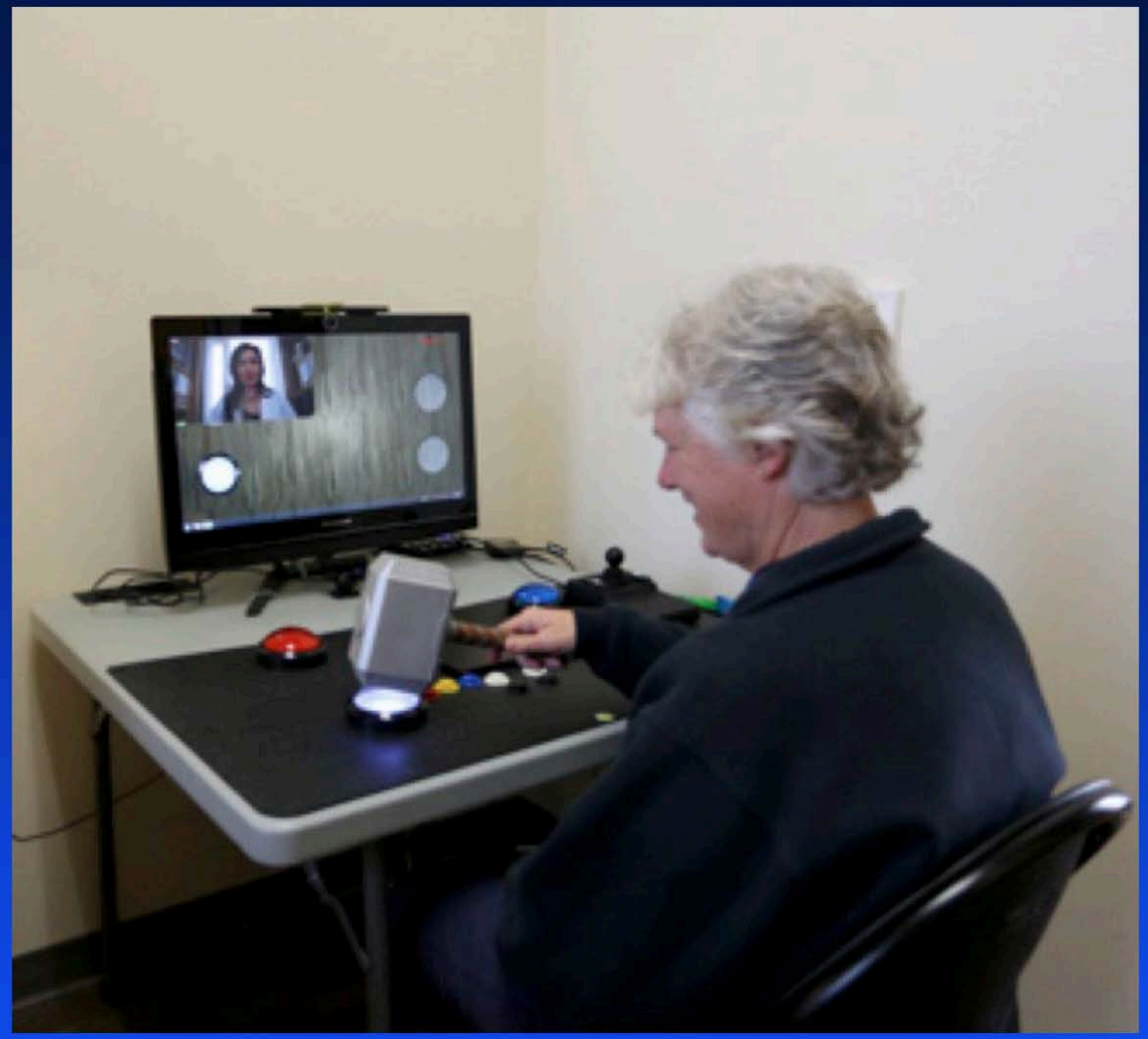
- Time: GTN worse when given very early



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

clinicaltrials.gov NCT02360488

Telerehab Trial

NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

Steve Cramer, UC Irvine

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,

Steve Cramer, UC Irvine

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

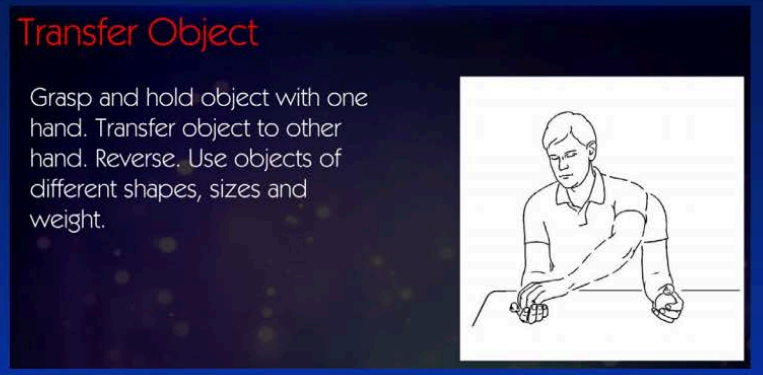
Telerehabilitation

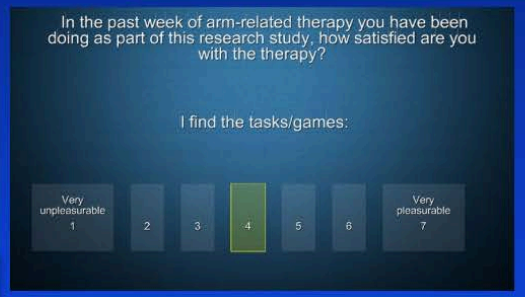
- Study team delivered a telerehabilitation system to the home
- **18 supervised treatment sessions** (70 minutes)
  --In the home, 30 min therapist videoconference at start
- **18 unsupervised treatment sessions** (70 minutes)
  --In the home, using telerehab system (no therapist contact)

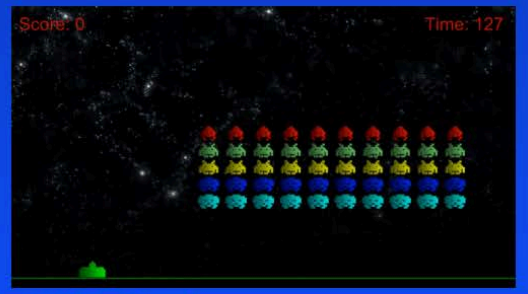
Games could be adjusted in relation to motor control, e.g., movement speed, timing, planning, range of motion, target size, cognitive demand, hemifield bias, bimanual, sustained, proximal vs. distal, and 1st person vs. 3rd person perspective

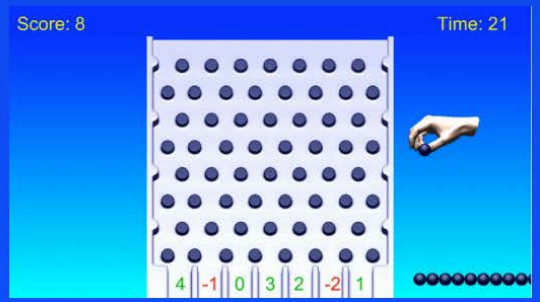
Telerehabilitation

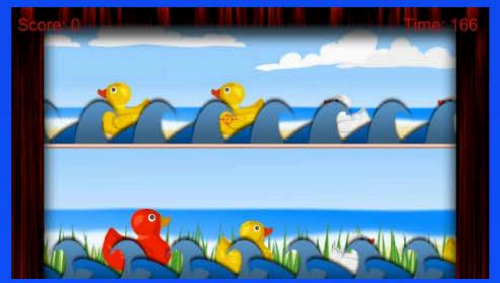
Diet	Stroke Facts	Stroke Risk Factors	Effects of Stroke	Exercise
$1000	$1000	$1000	$1000	$1000
$2000	$2000	$2000	$2000	$2000
$3000	$3000	$3000	$3000	$3000
$4000	$4000	$4000	$4000	$4000
$5000	$5000	$5000	$5000	$5000

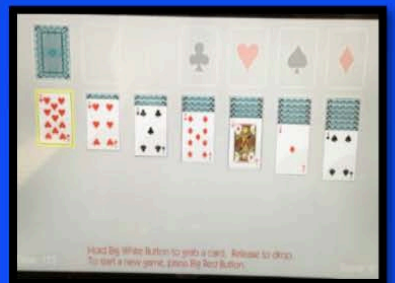


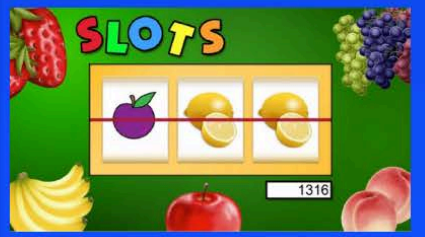










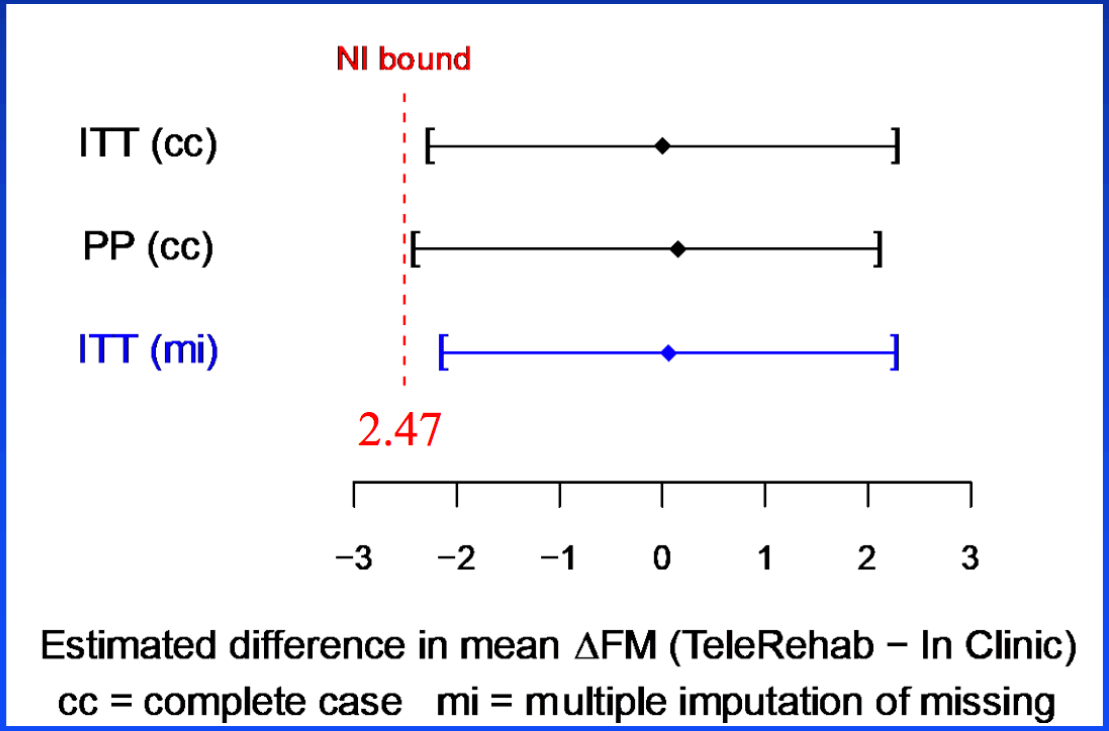


Results

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

Hamidreza Saber, Babak Navi, Hooman Kamel, Conrad W. Liang, Peng Roc Chen, Spiros L. Blackburn, Albert J. Yoo, Farhaan S. Vahidy, Sean I. Savitz, **Sunil A. Sheth**

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Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association | American Stroke Association

UTHealth
The University of Texas Health Science Center at Houston
Institute for Stroke and Cerebrovascular Disease

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.

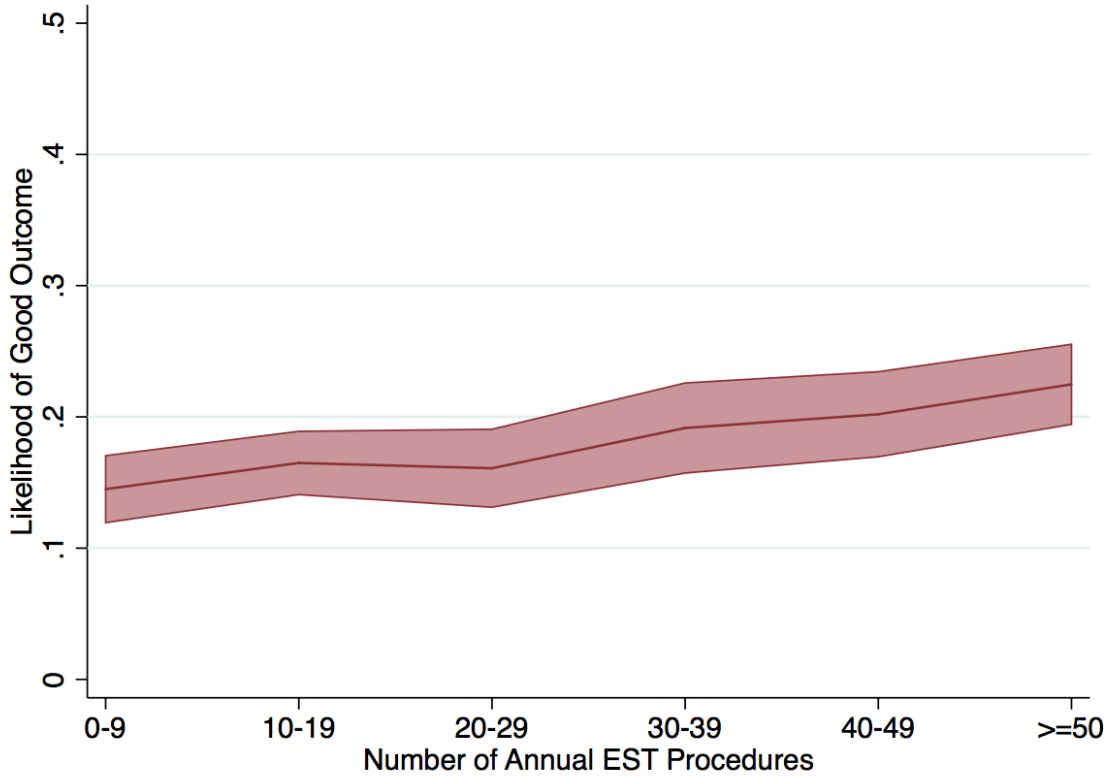
Methods:
Patients were identified using ICD-9 and ICD-10 diagnosis and procedure codes. Ischemic stroke was defined using previously validated codes. EST was defined as procedure code 39.74 or 03CG3ZZ and a corresponding code for ischemic stroke. IV tPA treatment was defined as procedure code 99.10 or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

Annual Trends - Florida



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

Ashkan Shoamanesh, Robert G. Hart, Scott E. Kasner, Eric E. Smith, Joan Marti-Fabregas, Yan Yun Liu, Shinichiro Uchiyama, Robert Mikulik, Roland Veltkamp, George Ntaios, Keith Muir, Thalia S. Field, Gustavo C. Santo, Veronica Olavarria, Hardi Mundl, Helmi Lutsep, Scott D. Berkowitz and Mukul Sharma

on behalf of the NAVIGATE ESUS Investigators

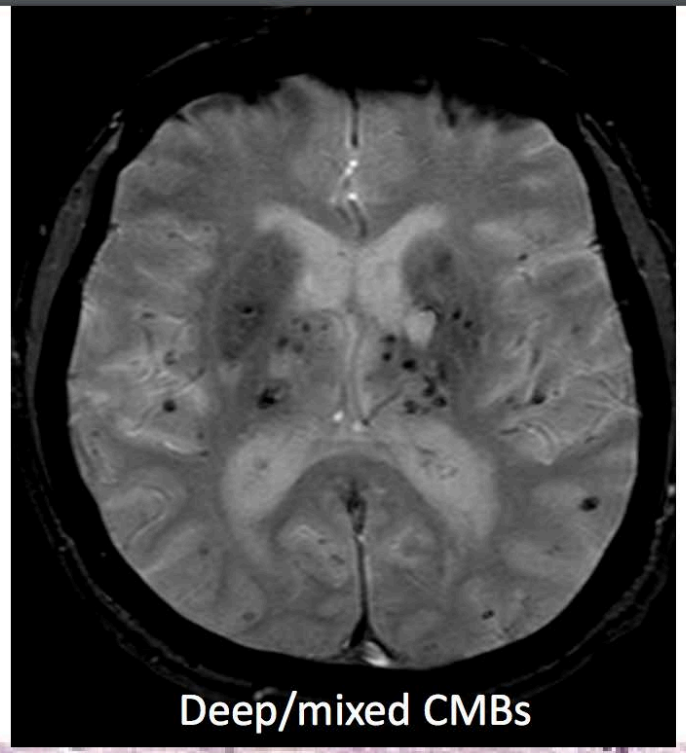
McMaster University

CSC CNC Canadian Stroke Consortium Consortium Neurovasculaire Canadien

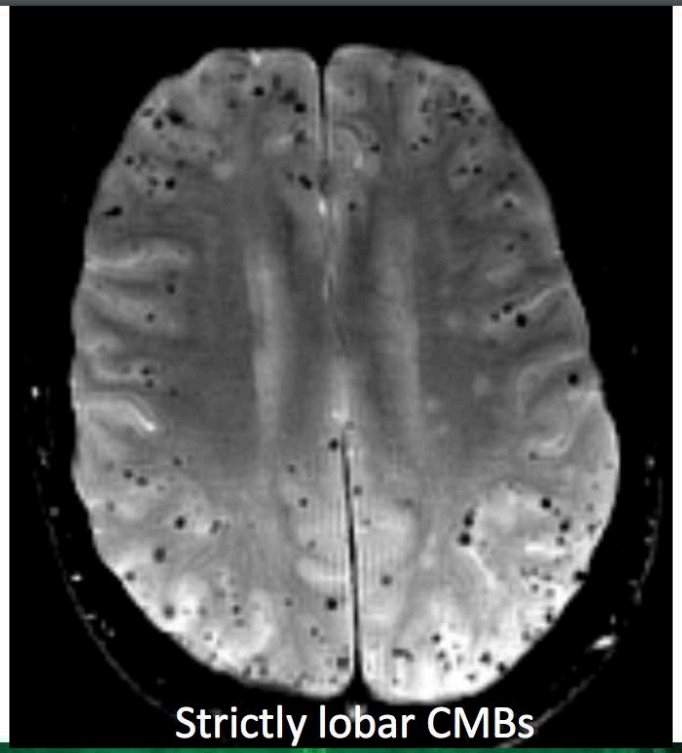
CoHESIVE

PHRI

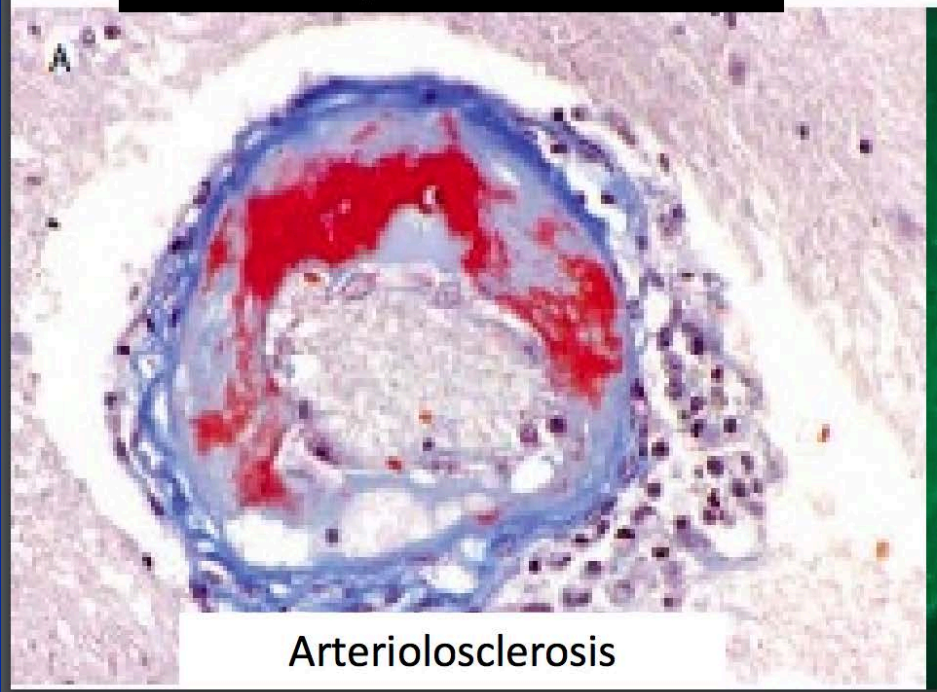
Hamilton Health Sciences



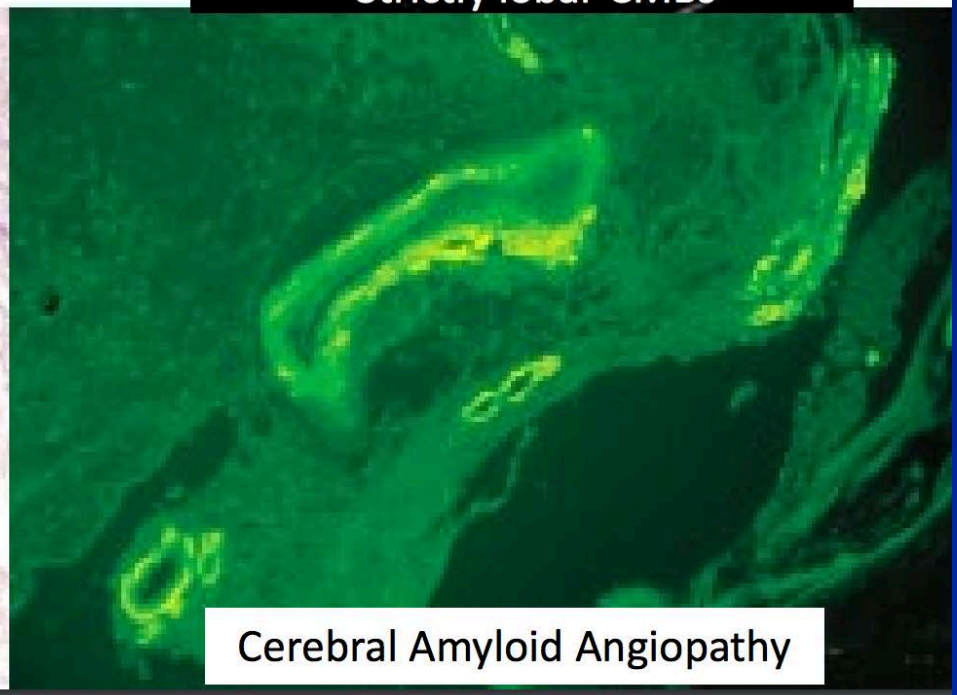
Deep/mixed CMBs



Strictly lobar CMBs



Arteriolosclerosis



Cerebral Amyloid Angiopathy

- 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.

Pregnancy-related stroke more common among black women

- 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

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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


Mahalo