NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

NEWSLETTER

NOVEMBER 2023 | VOLUME 2 | ISSUE 11

FASTEST

FVIIa for Acute hemorrhagic Stroke

Administered at Earliest Time

Issue Contents:

Message from Dr. Broderick

As we entered the last months of the calendar year, we wanted to remind all of our centers of the yearly recruitment awards for each country. We also will be having an interim analysis in very early 2024 so more patients enrolled will help us provide the best data for this analysis.

Here's to hoping the enrollment momentum continues and increases as the year ends and we get a fast start into 2024!!

Joseph Broderick, MD
Director NIH StrokeNet
Director UC Gardner Neuroscience Institute
FASTEST PI

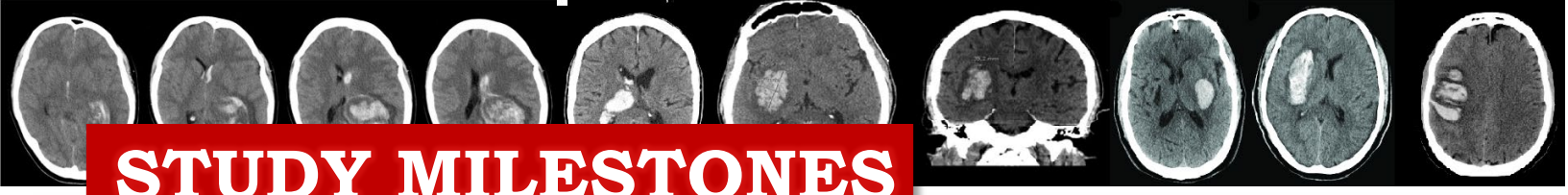
Please join us for the *FASTEST* Monthly Webinar

Wednesday November 15th, 2:00-3:00 pm EST

- Dr. Subramanian and his team from Queens Medical Centre, Nottingham, United Kingdom will be discussing case at their site.
- Dr. Paipa Merchan and her team from Bellvitge University Hospital, Barcelona, Spain will be discussing case at their site.
- Update from DSMB meeting in October.
- Repeat scan before any planned surgery in first 24 hours.
- Discussion about recording study drug wastage in WebDCU

Join Zoom Meeting
https://nam11.safelinks.protection.outlook.com/?url=https%3A%2F%2Fucincinnati.zoom.us%2Fj%2F91270599326&data=05%7C01%7Cquadrisd%40ucmail.uc.edu%7C59de671893534b5f411808db91e5229c%7Cf5222e6c5fc648eb8f0373db18203b63%7C0%7C0%7C638264185548573076%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C3000%7C%7C%7C&sdata=E5dRFfb7oIW1z8MCqQ%2Bbz5zs%2Fb6N1KbkElfCvsgt6NQ%3D&reserved=0

Prior presentations and slides are available at, https://www.nihstrokenet.org/fastest/webinars



STUDY MILESTONES

Total Sites Released to Enroll: **78** (**44** USA, **34** OUS: **6** Germany, **14** Japan, **4** Spain, **6** Canadian, **4** UK)

Total MSUs Released to Enroll: **12** (**10** US and **2** OUS)

Total Randomization = **305**

- US Randomizations: **83**
- International randomizations: **223** (**150** Japan, **36** Canadian, **20** Spain, **11** Germany, **5** UK)

Randomization last month = **29**
Total Screen Failures = **850**
Subjects Randomized by MSU = **12**
Subjects Terminated Early = **1**
eConsent Used = **6**
Remote Consent Used = **7**

CALENDAR OF EVENTS

Upcoming *FASTEST* Monthly Webinar: **Wednesday, November 15th, @ 2:00-3:00 pm EST**

FASTEST study team office hours: **Monday, November 20th, @ 2:00-3:00 pm**

IMPORTANT NOTE

FASTEST Imaging Reminders

Submit all head imaging performed as SOC within 30 hours from stroke onset to IMC (i.e., NCCT, CTA, MRI if performed). Includes:

- Baseline/first scan obtained either in ED or MSU to determine trial eligibility AND prior to study product administration.
- 24 (+/6) hours from stroke onset follow-up scan
- "Unscheduled" scan obtained for clinical deterioration or immediately prior to any surgical intervention (i.e., surgical removal of ICH or IVC placement) if planned prior to 24-hour scan.

*****Failure to obtain a pre-op scan results in missing imaging endpoint (i.e., ability to calculate ICH growth between baseline scan and unscheduled pre-op scan)**

Imaging must be submitted within 5-7 business days of subject randomization via the Ambra Health® platform.

- Also includes submission of WebDCU F502 which is needed to process scans.

***Confirmation of receipt of ALL imaging is one of the requirements in triggering "Baseline through 24 hr. Payment" to your site.

Pharmacy Reminders for PSCs

- There have been recent reports of temperature excursions at certain sites related to the storage of the study drug within the pharmacy. We strongly encourage all site PSCs to proactively engage with their trial pharmacist. Regular communication and periodic checks with the pharmacist will help ensure the consistent monitoring of temperature conditions and mitigate the risk of excursions.
- The TERF needs to be submitted to the NCC project manager and Strokenet central pharmacy as soon as possible.
- The site pharmacists should remove the effected study drug by filling out the WebDCU form in a timely manner in order to trigger a resupply. The sites are advised to add more people to the DOA in order to expedite the process of documenting things in WebDCU if necessary.

New Sites…Welcome Aboard!

The following new sites were **released to enroll** in the *FASTEST* study during the last month.

University Hospital Erlangen, Erlangen, Germany

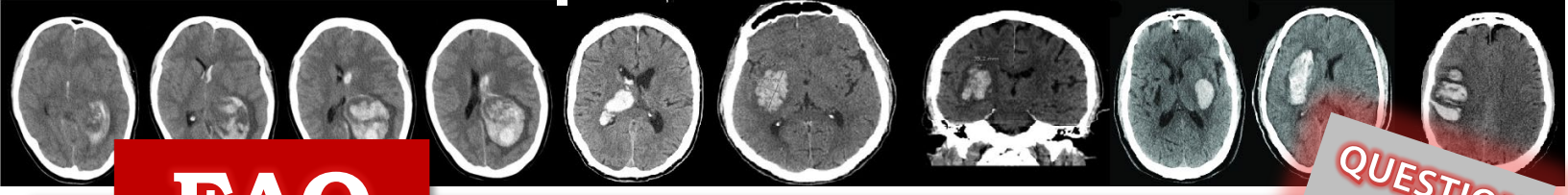
Site PI:
Joji KURAMATSU, MD

Congratulations on 1st Enrollment!!!

Congratulations to Dr. John LIANG and his team at the Mount Sinai Hospital, New York, NY and Mount Sinai West, New York, NYfor enrolling their first subject in FASTEST.

Congratulations to Dr. Christopher STREIB and his team at the M Health Fairview St. John's Hospital, Maplewood, MN for enrolling their first subject in FASTEST.

Congratulations to Dr. Elizabeth LIPTRAP and her team at the University of Alabama Hospital, Birmingham, AL for enrolling their first subject in FASTEST.



FAQ

QUESTION CORNER

Q: Can the baseline troponin be a "point of care" troponin? This is what is ordered and resulted for most of our stroke alert patients.
A: Yes, the base line troponin is usually the "point of care" troponin done for stroke patients and is reported in F105-Laboratory Tests.

Q: Can we use the GCS from the ER staff?
A: Yes, as long as the GCS from the ER staff (licensed physician or nurse) is recorded in your EMR notes.

Q: If site fail to utilize the lowest kit number during the randomization, will that cause any queries when the research staff completes the enrolment form in WebDCU?
A: No, you will not get queriers in WebDCU for not using the lowest kit number.

Q: Can we use estimated weight to calculate the IP dose?
A: Actual weight is preferred, but estimated weight **is acceptable.** Estimated body weight is appropriate to use for dosage determination, especially since we can't always wait for a stroke patient to be weighed. However, to ensure that there is no overdose and to calculate the dose check **we do need the sites to report the subject's actual weight** in the WebDCU. This can be done at any time during their hospitalization.

Q: When reporting adverse event outcome, when would I select 'Unknown'?
A: An adverse event should only be unknown when a subject is lost to follow up and the medical record does not confirm the outcome. If a subject completes the study through the Day 180 Visit, another outcome must be selected. Remember to check-in on all previously reported ongoing events at each study visit.

Q: The 180 day follow up of our FASTEST subject. The participant has a clinic visit planned this Wednesday and is unlikely we will be able to arrange a in person follow up in October. We would need to do the follow up remote. Would it be preferred to do a mRS and EQ-5D in person out of window (3 weeks early) in the clinic as well or do we just wait to do these remote?
A: The protocol encourages in-person follow up at 180 days. However, a remote follow up can also be done if in-person is not possible.

Q: I have recently concluded the 30-Day visit for the subject and learned that they sought medical attention at an urgent care facility due to hypertension and an elevated morning blood sugar. During the visit, the healthcare provider adjusted the dosage of medications for both blood pressure and diabetes management. I am seeking clarification regarding whether this should be documented as an Adverse Event (AE). It's worth noting that both hypertension and diabetes are pre-existing medical conditions within the subject's medical history, which leads us to assume that it may not qualify as an AE. Any guidance or clarification would be greatly appreciated.
A: As per study protocol and MOP any adverse events (AE) are to be reported only during the first 4 days. However, all serious adverse events (SAE) are to be reported throughout the study period (until 180 days). In your case at 30-day follow-up, depends on if the Site PI deems this to be an SAE or just an AE. If the Site PI considers this an SAE and reportable, please report it. Otherwise, AE are not required to be reported at 30 days.

Please send in your questions and we will address them accordingly and share with others in the next Newsletter.

SHOUT OUTS!!

Congratulations to all our US sites that have completed their EFIC reports and gained Advarra full study approval. UPDATE?

Thank you to the sites recently released to enroll for their hard work:

1. **Kaiser Permanente Fontana, CA**
2. **Kaiser Permanente West LA, CA**

Thank you to the sites that have gotten CIRB/REB/EC approval and preparing for readiness:

1. **University of Florida Health Shands, FL**

Top Enrolling Site

Congratulations to **Kobe City Medical Center General Hospital, Kobe, Japan** for being the highest enrolling site in the study.

Subjects enrolled = 36!!

Congratulations to Enrolling Sites last Month!

Kobe City Medical Center General Hospital, Kobe, Japan	3 Subjects
National Cerebral and Cardiovascular Center, Osaka, Japan	5 Subjects
Toranomon Hospital, Tokyo, Japan	3 Subjects
Kagoshima City Hospital, Kagoshima, Japan	2 Subjects
KMU University Hospital, Osaka, Japan	1 Subject
Iwate Prefectural Central Hospital, Morioka, Japan	1 Subject
Nakamura Memorial Hospital, Sapporo, Japan	2 Subjects
Niigata City General Hospital, Niigata, Japan	1 Subject
NHO Osaka National Hospital, Osaka, Japan	1 Subject
University of Alberta Hospital, Edmonton, AB, Canada	1 Subject
Queens Medical Centre, Nottingham, United Kingdom	1 Subject
Riverside Methodist Hospital, Columbus, OH	1 Subject
Temple University Hospital, Philadelphia, PA	1 Subject
The Mount Sinai Hospital & Mount Sinai West, New York, NY	2 Subjects
M Health Fairview St. John's Hospital, Maplewood, MN	1 Subject
Riverside Methodist Hospital, Columbus, OH	1 Subject
University of Alabama Hospital, Birmingham, AL	1 Subject
Mills Peninsula Medical Center, Burlingame, CA	1 Subject

SCIENCE CORNER

ARTICLE OF THE MONTH

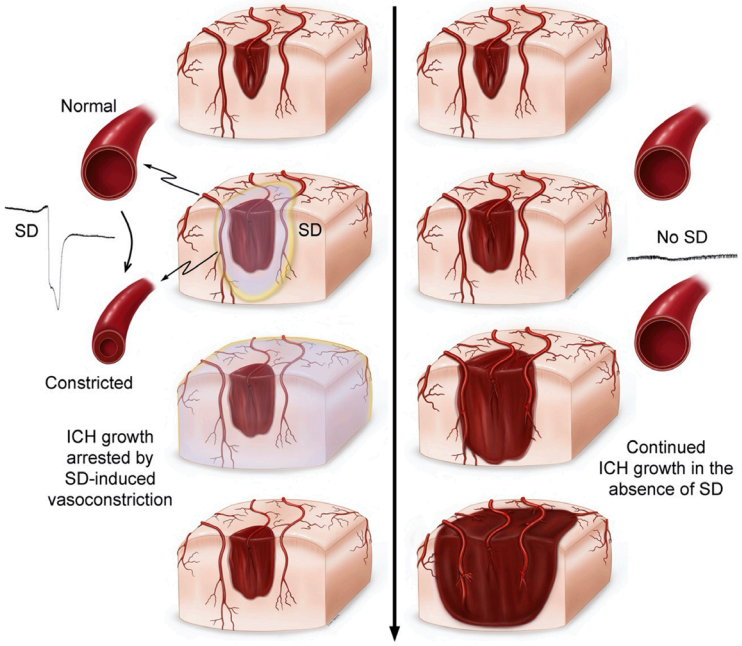
Depolarizations Suppress Hematoma Growth in Hyperacute Intracerebral Hemorrhage in Mice

Paul Fischer, Isra Tamim, Kazutaka Sugimoto, Andreia Morais, Takahiko Imai, Tsubasa Takizawa, Tao Qin, Frieder Schlunk, Matthias Endres, Mohammad A. Yaseen, David Y. Chung, Sava Sakadzic and Cenk Ayata

Originally published23 Aug 2023https://doi.org/10.1161/STROKEAHA.123.042632Stroke. 2023;54:2640–2651

Background:

Spreading depolarizations (SDs) occur in all types of brain injury and may be associated with detrimental effects in ischemic stroke and subarachnoid hemorrhage. While rapid hematoma growth during intracerebral hemorrhage triggers SDs, their role in intracerebral hemorrhage is unknown.



Here we challenge the dogma of spreading depolarizations (SD) being detrimental to the progression of brain injury. Using optical imaging and electrophysiology, we show that SDs limit hematoma growth in hyperacute intracerebral hemorrhage (ICH) and reduce hematoma volume by ~40-60%. Moreover, we implicate the vasoconstrictive effect of SDs on cerebral arteries as the likely mechanism of slowing hematoma growth using laser speckle flowmetry. Highlighting the clinical translational significance, we show that this effect is most robust under hypertensive conditions. Altogether, our data suggest that SD is an innate feedback mechanism in ICH.

Methods:

We used intrinsic optical signal and laser speckle imaging, combined with electrocorticography, to investigate the effects of SD on hematoma growth during the hyperacute phase (0–4 hours) after intracortical collagenase injection in mice. Hematoma expansion, SDs, and cerebral blood flow were simultaneously monitored under normotensive and hypertensive conditions.

Results:

Spontaneous SDs erupted from the vicinity of the hematoma during rapid hematoma growth. We found that hematoma growth slowed down by >60% immediately after an SD. This effect was even stronger in hypertensive animals with faster hematoma growth. To establish causation, we exogenously induced SDs (every 30 minutes) at a remote site by topical potassium chloride application and found reduced hematoma growth rate and final hemorrhage volume (18.2±5.8 versus 10.7±4.1 mm3). Analysis of cerebral blood flow using laser speckle flowmetry revealed that suppression of hematoma growth by spontaneous or induced SDs coincided and correlated with the characteristic oligemia in the wake of SD, implicating the vasoconstrictive effect of SD as one potential mechanism of action.

Conclusions:

The strongest association between HE and outcome was observed in patients with smaller initial volume experiencing severe HE. These findings may inform clinical trial design and guide clinicians in selecting patients for anti-expansion therapies.

HELPFUL REMINDERS & TIPS

For Project Managers, Study Coordinators & Study Teams

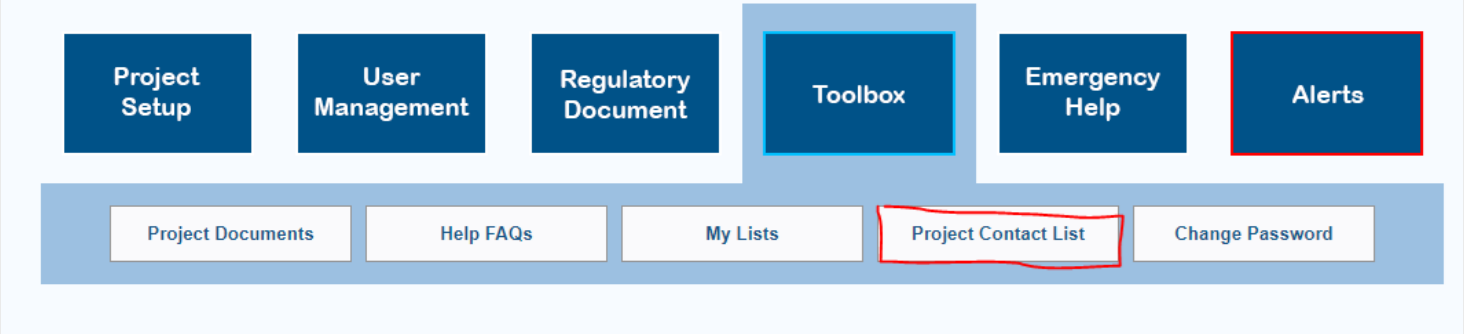
- **Updating 1572:** Compliance with regulatory requirements mandates that every modification to a 1572 form necessitates the PI signature to acknowledge the alteration. It is essential to understand that updates to an existing 1572 are not permissible; instead, a new 1572 form must be created for each update. Consequently, the PI is required to sign a new 1572 form with every update made.

- **Temperature excursion and monitoring: Please be very vigilant about temperature excursion and temperature monitoring documentation.** FASTEST sites using the ***Emerald temperature loggers*** provided by us for their MSU or ED we will be sending out weekly reminder email every Friday to the PSC. Checking once a week should ensure careful monitoring of temperature excursion and documentation, as well as avoiding the use of affected study drug.

- If kit that was affected was used for randomization it is advised to communicate with the subject to ensure that they are fully informed about the situation regarding the affected study drug. An update regarding this communication should be provided to the CIRB for their records (while reporting this deviation).

- **FASTEST is now operating under Version 7 of the Protocol.** Please sign and upload **PI Protocol v7 Training Attestation** and **new Protocol v7 Signature Page** to WebDCU.
  - It is mandatory for all PIs to sign a new **Training Attestation** for Protocol v7. By signing this attestation, the PI confirms that all individuals listed on the current DoA have received training on the updated protocol. Therefore, it is not necessary to collect a new training attestation from each investigator/study team member individually.
  - We kindly request all sites to maintain an internal training log as evidence that every individual has undergone training on the updated Protocol v7. This log will serve as documentation, which may be required during an FDA audit, to verify that the study team members have been sufficiently trained on the protocol updates.

- WebDCU have now included a "project contact list" feature, which contains all the important contact information that the site might require during the course of the trial. Sites can access it by navigating to FASTEST > ToolBox > Project Contact List.



From the *FASTEST* Central Pharmacy Team

- Instructions to fill out TERF from are in the toolbox in WebDCU.

- Kit #, DUN# and the Lot number could all be found in the 'Site Drug Kit Removing' section in the WebDCU.

- Please make sure to disseminate this newsletter to you site pharmacist/s too as it may contain helpful information regarding drug compounding, storage, accountability, etc.

INTERNATIONAL SITE OF THE MONTH

Iwate Prefectural Central Hospital, Morioka, Japan

Iwate Prefectural Central Hospital, situated in Morioka, Japan, stands as a pivotal institution in the region's healthcare landscape. Renowned for its commitment to providing comprehensive and cutting-edge medical services, the hospital plays a crucial role in promoting health and well-being within the community. Morioka, the capital city of Iwate Prefecture, benefits significantly from the hospital's multifaceted approach to healthcare, combining state-of-the-art facilities with a dedicated and highly skilled medical staff.

The hospital's mission encompasses a wide spectrum of medical services, ranging from routine check-ups to specialized treatments and surgeries. With a focus on patient-centered care, Iwate Prefectural Central Hospital emphasizes accessibility, affordability, and a holistic approach to health.

The institution's commitment to continuous improvement is evident in its integration of the latest medical technologies and research advancements, ensuring that residents of Morioka and the surrounding areas have access to the best possible healthcare services.

Beyond its role as a medical facility, Iwate Prefectural Central Hospital is deeply engaged in community outreach and health education initiatives. These efforts contribute to raising awareness about preventive healthcare measures and fostering a healthier lifestyle among the local population. Through its various programs and partnerships, the hospital actively collaborates with the community to address health challenges and promote overall well-being, reflecting its dedication to serving as a cornerstone of health and healing in Morioka, Japan.

STUDY CONTACTS & USEFUL INFO

For any study related queries or help please reach out to ***FASTEST*** Project managers

International Sites: **Syed Quadri** (quadrisd@ucmail.uc.edu)

United States Sites: **Emily Stinson** (stinsoey@ucmail.uc.edu)

FASTEST Clinical Hotline: 1-855-429-7050

For more information regarding the ***FASTEST*** study please visit : https://www.nihstrokenet.org/fastest/home

For prior ***FASTEST*** Presentations and Webinars slides and recordings visit: https://www.nihstrokenet.org/fastest/webinars

For more information regarding the StrokeNet Trials please visit: https://www.nihstrokenet.org/