Pericyte Control of the Microcirculation in Ischemic Brain

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Abstract Body: Introduction: Despite successful recanalization of the occluded cerebral artery using tissue plasminogen activator or endovascular devices, close to half of treated patients still end up with a poor clinical outcome. This may in part be due to a microvascular perfusion deficit termed “no-reflow”.

Hypothesis: We tested the hypothesis that pericyte contraction restricts capillary RBC flux and promotes leukocyte adhesion after experimental stroke in mice; contributing to microvascular no-reflow. We also determined if the vasoprotective eicosanoids epoxyeicosatrienoic acids (EETs) can prevent no-reflow by relaxing pericytes.

Methods: The microcirculation in the peri-infarct region of wild-type (WT), Tie2-GFP/NG2-DsRed mice, and mice with endothelial overexpression of EETs synthase (Tie2-CYP2J2) was imaged in-vivo with two-photon microscopy and optical microangiography (OMAG). Changes in microvascular blood flow, capillary diameter, RBC flux and leukocyte adhesion were assessed at 24 hours after 1-hour middle cerebral artery occlusion (MCAO). In separate mice, the EETs antagonist 14,15-Epoxyeicosa-5(Z)-enoic acid (14,15-EEZE) or vehicle was microinjected into the cortex through a craniotomy using a picospritzer to investigate role of EETs in pericyte contraction.

Results: Microvascular perfusion was markedly reduced after MCAO in wild-type (WT), but not Tie2-CYP2J2 mice. Capillaries directly underneath pericytes underwent a dual response, with some capillaries increasing, while others reducing diameter. Capillary constriction was associated with reduced RBC flux and leukocyte adhesion, whereas dilated capillaries were associated with blood-brain barrier disruption. Application of 14,15-EEZE directly to pericytes induced capillary contraction.

Conclusions: We conclude that pericytes play an important role in maintaining capillary blood flow and preventing leukocyte adhesion, and that pericyte injury after stroke contributes to microvascular no-reflow. Strategies to augment EETs may prevent the expansion of ischemic infarct, in part by preventing microvascular no-reflow.
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Presentation Number: LBP2

Publishing Title: Dual Antiplatelet Therapy May Decrease 1-year Stroke Recurrence for Patients With Minor Stroke or Transient Ischemic Attack and Intracranial Arterial Stenosis: Subgroup Analysis of CHANCE

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Abstract Body: Background and Objective: Recently, the Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial reported that the early benefit of clopidogrel-aspirin treatment in reducing the risk of subsequent stroke persisted for the duration of 1-year of follow-up. The aim of this subgroup analysis was to discuss whether dual antiplatelet therapy could decrease the 1-year stroke recurrence in patients with minor stroke or transient ischemic attack and intracranial arterial stenosis.

Methods: In this subgroup analysis, we assessed the interaction of the treatment effects of clopidogrel plus aspirin versus aspirin alone among patients with and without ICAS, identified by magnetic resonance angiography (MRA). CHANCE is registered with ClinicalTrials.gov, identifier NCT00979589.

Results: Of the 5,170 patients enrolled in the CHANCE trial, 481 (44.2%) patients with intracranial stenosis or occlusion, 231(48.02%) received dual antiplatelet therapy among them. Patients with ICAS had higher rates of recurrent stroke (14.14% vs 6.25%, p<0.0001) at 1 year, compared with those without ICAS. For patients with intracranial stenosis or occlusion, one year stroke recurrence were 30 (12.99%) in clopidogrel plus aspirin group and 38(15.20%) placebo plus aspirin group. But there was no statistically significant evidence for the existence of the treatment by presence of ICAS interaction on either the primary outcome of any stroke (interaction p=0.613) or the safety outcome of any bleeding event (interaction p=0.300).

Conclusions: The results indicated lower rate of 1-year recurrent stroke in dual antiplatelet group for patients with intracranial stenosis or occlusion. Studies in other populations and subsequent analysis with adequate power are warranted to further verify such findings.

**Presentation Number:** LBP3

**Publishing Title:** Kaiser Stroke EXPRESS Program - Expediting the Process of Evaluating & Stopping Stroke

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**Abstract Body:**

**Background:** Studies showed that faster treatment with tPA in acute ischemic stroke was associated with better outcomes. Recent randomized trials showed convincing benefits of endovascular therapy (EST) plus tPA for appropriate patients when treated promptly. With these goals in mind, Kaiser Permanente Northern California (KPNC) redesigned its acute stroke care work flow for the entire region. We examined the effect of this new regional stroke program on door-to-needle (DTN) time.

**Methods:** KPNC serves 3.8+ million members with 21 primary stroke centers spread over 17,000 square miles. KPNC redesigned its acute stroke care processes: 1) to allow a core group of vascular neurologists to be involved with all stroke alerts across the region early in the process via teleneurology; 2) to expedite the evaluation and determination for tPA; and 3) to speed up the evaluation for large vessel occlusion to allow timely transfer of appropriate patients to preferred centers for EST. On September 16, 2015, KPNC rolled out the EXPRESS program at its first 2 stroke centers with the goal of including all stroke centers by end of 2015. We assessed acute stroke processes pre- and post-going-live date for the new program.

**Results:** In 2015, there was an average of 28 stroke alerts per month at the 2 medical centers, unchanged in pre- or post-EXPRESS. Pre-EXPRESS, there were 44 tPA cases with an average age of 72.3 ± 13.6 years and 56.8% female compared to 15 tPA cases in the post-EXPRESS period with an average age of 77.9 ± 13.2 years (p=0.17) and 53.3% female. The monthly tPA rate was higher in post-EXPRESS period (39.3% vs. 16.4%). After starting the new work flow, the average DTN time decreased significantly (32.9 ± 10.7 minutes vs. 62.2 ± 27.7 minutes, p=0.0002) [Figure].

**Conclusions:** Preliminarily, we were able to achieve a higher rate of tPA treatment and shorter DTN time after the start of the new Stroke EXPRESS program. Close monitoring will continue as all 21 centers adopt the new stroke alert work flow.
Author Disclosure Block:  M.N. Nguyen-Huynh: Employment; Significant; The Permanente Medical Group. J. Klingman: Employment; Significant; The Permanente Medical Group.
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Presentation Number: LBP4

Publishing Title: Targeted Lipid Profiling Discovers Plasma Markers of Large Vessel Infarction: Interim Results of the ASPIRE-Stroke Study

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Abstract Body: BACKGROUND: With the release of the 2015 AHA Guidelines regarding endovascular stroke therapy, rapidly identifying and transporting patients with large vessel occlusions to medical centers capable of endovascular therapy has become more important than ever. A blood test that could aid in the initial evaluation could greatly improve the accuracy of the assessment. We previously showed circulating sphingolipids (SL) may serve as useful plasma markers of acute brain injury. The ASPIRE-Stroke trial is designed to validate this approach in a large clinical cohort.

METHODS: We performed targeted lipid profiling using SL-specific extraction methods followed by HPLC-MS/MS in plasma collected at the time of hospital arrival in consecutive patients presenting via the acute stroke protocol. Partial least squares discriminant analysis was used to derive a classification model from the SL plasma concentrations.

RESULTS: Among 111 patients presenting to our hospital with symptoms concerning for acute stroke, 51% were female, mean age was 72 ± 14. 48 (43%) were diagnosed with stroke, 15 (14%) TIA, 42 (38%) stroke mimics, and 6 (5%) intracerebral hemorrhage. Median time from symptom onset to blood collection was 150 minutes (IQR 60-285). Among patients diagnosed with ischemic stroke, mean NIHSS was 7 ± 7, DWI volume was 22 ± 54, 30% had large vessel infarcts and 70% had non large vessel vessel infarcts. Among the 71 SLs definitively identified, 21 were ceramide (Cer) and 40 were sphingomyelin (SM) species. Using a panel of 7 SLs (4 SMs and 3 Cers), patients with large artery infarcts could be differentiated from patients with stroke mimics and non large-vessel infarcts with very good accuracy (C-statistic 0.78). ROC Curve and sensitivity/specificity curves are shown in Figure 1.

CONCLUSIONS: Sphingolipid profiling can identify patients with large artery infarcts with very good accuracy at early time points after onset of acute stroke syndromes.
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Presentation Number: LBP5

Publishing Title: The “Uncertainty Principle” as an Entry Criterion in Stroke Clinical Trials: Bias Towards Null Findings

Author Block: Annasha Vyas, Jeffrey Saver, Univ of California-Los Angeles, Los Angeles, CA

Abstract Body: Hypothesis: Under different conditions of physician personal equipoise, the use of the “uncertainty principle” as an entry criterion in stroke clinical trials may bias trial results.

Background: In addition to standard clinical trial entry criteria, “uncertainty principle (UP)” randomized trials instruct investigators to only enroll patients when the individual enrolling doctor is uncertain whether that particular patient will benefit from the tested treatment. The use of personal equipoise (“gray zone”) as an enrollment criterion in stroke trials (e.g. EC-IC bypass, ECST, and IST-3) has engendered controversy.

Methods: We analyzed the impact of UP randomization in model stroke populations under four conditions: 1) enrollment without UP, and enrollment using UP by 2) treatment enthusiasts, 3) treatment skeptics, and 4) treatment agnostics.

Results: When physicians lacked insight into the population that would benefit from therapy, treatment effect estimates of UP randomized trials matched those not using the UP and accorded with true treatment effects. However, when physicians did have such insight, use of the UP biased findings toward the null. For a model with true treatment effect improving outcomes by relative risk 1.3, UP trials estimated treatment effects by relative risk 1.0 with treatment agnostics, 1.1 with skeptics, and .91 with enthusiasts.

Conclusions: When investigators accurately judge which patients will benefit from therapy, using the uncertainty principle can substantially influence randomized trials toward null findings for treatments that are actually beneficial. This bias should be considered when interpreting stroke trial results.

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Presentation Number: LBP6

Publishing Title: Incidence and 30-day Case-fatality Rate of First-Ever Stroke and Transient Ischaemic Attack: Program for the Epidemiological Evaluation of Stroke in Tandil, Argentina (PREVISTA)

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Abstract Body: Background: Population-based data about stroke in Latin America is scarce. We assessed first-ever stroke and transient ischaemic attack incidence, and 30-day case fatality rates in Tandil, Argentina.

Methods: PREVISTA was developed according to the criteria for studies of stroke incidence proposed by Sudlow and Warlow and by using the World Health Organization (WHO)s Standardized Tools for Stroke Surveillance (WHO-STEPS) manual. We prospectively identified all possible stroke and transient ischaemic attack cases from overlapping sources between May 1, 2013 and April 30, 2015 in Tandil, Argentina. We calculated crude and adjusted incidence rates from the population of Tandil according to the 2010 National Census.
Findings: Of 543 events identified, 334 were first-ever strokes and 108 first-ever transient ischaemic attacks. Age-adjusted (Segis World population) incidence rate per 100000 was 765 (95%CI 678-859) for first-ever stroke and 251 (95%CI 202-307) for first-ever transient ischaemic attack. Age-adjusted rates per 100000 by first-ever stroke type were: 561 (95%CI 488-642) for ischaemic stroke, 135 (95%CI 99-179) for haemorrhagic stroke and 49 (95%CI 27-81) for subaracnoid haemorrhage. Thirty-day case fatality rate was 156% (95% CI 125-192) for all first-ever events, 147% (95% CI 108-195) for IS, 241% (95% CI 142-366) for HS, and 19% (95% CI 04-58) for TIA. Figure shows Kaplan Meier survival analysis according to incident vs recurrent, type of stroke, gender and age quintiles.

Interpretation: PREVISTA is the first prospective population-based study of stroke and transient ischaemic attack incidence and mortality conducted in Argentina. First-ever stroke incidence was lower than in prior community-based studies in Latin America, but incidence of first-ever transient ischaemic attack was higher. 30-day case fatality rates were similar to those reported in other population-based Latin American studies.

**Abstract Body:**

**INTRODUCTION:** It is firmly established that management of acute stroke at dedicated stroke units (SUs) improves functioning and survival. Although guidelines recommend SU admission as 1st level of care for all patients with acute stroke, quality registers show that many patients are treated at non-SU wards. The effects of reducing hospital bed capacity, commonly due to economic constraints, on quality of stroke care have received little attention. The primary objective of the study was to investigate if acute stroke patients are less likely to be directly admitted to an SU when hospital beds are scarce. A secondary objective was to compare performance across hospitals.

**METHODS:** This registry study comprised data on patients with acute stroke admitted to 14 out of 72 Swedish emergency hospitals in 2011-2014. Data from The Swedish Stroke Register (Riksstroke) were linked to day-to-day data on hospital bed occupancy (at 6 am). SU care included care at ICU and neurosurgery facilities. Directed Acyclic Graphs were constructed to reveal confounding variables. Nested multivariable models (logistic regression) were developed to adjust for confounding and evaluate hospital performance (hospital bed occupancy kept constant). Covariates adjusted for included sex, age, prior stroke, thrombolysis, level of consciousness and stroke type.

**RESULTS:** A total of 13,955 hospital admissions were included. The odds of direct admission to an SU decreased by 1.5% for every percentage increase in hospital bed occupancy exceeding 90% (OR 0.985, 95% CI 0.978-0.992). The best-performing hospital exhibited an odds-ratio of 3.8 (95% CI 2.6-5.5) for admitting patients to an SU directly, compared to the reference (the participating hospital with most stroke admissions during the period).

**CONCLUSIONS:** Our study is, to our knowledge, the first to show that patients with acute stroke were less likely to be admitted directly to an SU as 1st level of care at days when hospital beds were scarce. Hospital differences suggest that organizational changes at the hospital level may have important effects on the quality of stroke care.

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Presentation Number: LBP8

Publishing Title: Interim Analysis of an Australian Telestroke Service Using Multimodal CT Imaging Decision Assistance

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Abstract Body: Background: Telestroke services can increase stroke therapy access in rural areas. The use of advanced CT imaging for patient selection may improve the likelihood of favourable outcomes from therapy. We describe the first application of multimodal CT in tele-reperfusion treatment.

Methods: A telestroke service supported by multimodal CT imaging and automated perfusion image analysis was implemented in a rural hospital in Australia. After 21 months, a preliminary evaluation of the service was conducted using a pre- versus post- implementation quasi-experimental design. Treatment rates for stroke patients in the spoke catchment for the pre and post implementation periods were compared. Rates of symptomatic intracranial haemorrhage, 90 day modified Rankin scale scores, door-CT, door-treatment and onset-treatment times were assessed and compared to a time-matched cohort of stroke patients treated at the hub centre.

Results: Using this system, 55 patients were assessed and 13 patients were thrombolysed. One patient (20% of large artery occlusions) was referred to the hub site for additional thrombectomy. The rate of administration of intravenous alteplase was 1% of all suspected stroke patients before implementation of the telestroke service compared to 3% following implementation (p = 0.06). Advanced CT imaging identified 15% of activations to be stroke mimics. Thirty per cent of patients achieved 90-day mRS ≤2 (95%CI 2-58%).

Conclusion: A telestroke service using advanced CT imaging for therapy decision assistance can be successfully implemented in regional Australia and can be used to guide acute stroke treatment decision-making and improve access to intravenous alteplase therapy.