Stroke Research 2014

Fen-Lei Chang, MD, PhD

Professor of Neurology, Indiana University School of Medicine – Fort Wayne
Medical Director, Parkview Stanley Wissman Stroke Center
Fort Wayne Neurology

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Disclosures:
Genentech and AstraZeneca: Principal Investigator
for clinical trials
• Research offers treatment options not available in general practice, the main goal however is to provide a sound foundation for future evidence based medical practice

• Potential treatment for mild stroke or TIA
  – PRISMS
  – SOCRATES
  – up to 24 hours after stroke onset

• IV tPA and intervention – Dr. Khatri
  – SWIFT PRIME

• It is important to remember that it is EXPERIMENTAL

• Patient safety is always the first priority

• All research opportunities started simply with a phone call to Parkview Research
Neuroprotection
Overcoming Failure of Translational Research from Bench to Bedside

• More than one thousand peer-reviewed publications on successful neuroprotection against stroke neural damage in various stroke models, but none so far proven to be useful in human clinical trials.

• Proposed reasons
  – Difference of stroke in human and animal models
  – Heterogeneity of stroke in human
  – Lack of sensitivity of outcome measures in human stroke research
  – Lack of clinical relevance of basic research such as pre-treatment, early reperfusion, and unrealistic dosing

• Needs for combination treatment with efficacy on blocking multiple ischemic pathways
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Translational Stroke Research

• First animal stroke model focused on penumbra, not on ischemic core

• Clinically relevant time window after stroke onset

• MCA occlusion, brain slice, and cell culture models

• Combination Rx:
  – Lamotrigene
  – Lovastatin
  – Minocycline

• Translational research
PRISMS

- Phase IIIb, double-blind study to evaluate Alteplase in patients with mild stroke
- Within 3 hours of stroke onset
- NIHSS $\leq 5$ and not clearly disabling
- Why? Many of these patients (around 30%) were significantly disabled upon evaluation at 3 months (mRS 2-6)
PRISMS
So Why So Many People with Significant Disability After Initial Mild Deficits??

- Stroke Progression from lost collaterals and/or increased thrombus
- Under-measured cognitive deficits by NIHSS
- Under-appreciated effect of observed deficits at time of presentation

“He worked a desk job for years and spent every night parked in his recliner. Let this be a wake-up call to the rest of us who live a sedentary lifestyle. Get active, or we'll all end up like him ... a sitting duck.”
Evaluate ASA vs Ticagrelor for patients with mild stroke or high risk TIA on vascular outcome including

1. Stroke
2. MI
3. Vascular death
SOCRATES

- Ticagrelor (Brilinta) is a platelet aggregation inhibitor
Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

Lars Wallentin, M.D., Ph.D., Richard C. Becker, M.D., Andrzej Budaj, M.D., Ph.D., Christopher P. Cannon, M.D., Håkan Emanuelsson, M.D., Ph.D., Claes Held, M.D., Ph.D., Jay Horwarth, M.D., Steen Husted, M.D., D.Sc., Stefan James, M.D., Ph.B., Hugo Katus, M.D., Kenneth W. Mahaffey, M.D., Benjamin M. Scirica, M.D., M.P.H., Allan Skene, Ph.D., Philippe Gabriel Steg, M.D., Robert F. Storey, M.D., D.M., and Robert A. Harrington, M.D., for the PLATO Investigators*

**Figure 1. Cumulative Kaplan–Meier Estimates of the Time to the First Adjudicated Occurrence of the Primary Efficacy End Point.**
The primary end point — a composite of death from vascular causes, myocardial infarction, or stroke — occurred significantly less often in the ticagrelor group than in the clopidogrel group (9.8% vs. 11.7% at 12 months; hazard ratio, 0.84; 95% confidence interval, 0.77 to 0.92; P<0.001).

**Figure 2. Cumulative Kaplan–Meier Estimates of the Time to the First Major Bleeding End Point, According to the Study Criteria.**
The time was estimated from the first dose of the study drug in the safety population. The hazard ratio for major bleeding, defined according to the study criteria, for the ticagrelor group as compared with the clopidogrel group was 1.04 (95% confidence interval, 0.95 to 1.13).
• **High risk TIA**
  - $ABCD^2 \geq 4$
  - Symptomatic intracranial arterial stenosis
  - Symptomatic ICA stenosis
  - Qualification includes findings on TCD, Carotid US, CT angiogram, or MR angiogram
Stroke risk was strongly associated with total score: 90-day stroke risks ranging from 20% with a score of 6-7 to < 1% with a score of 0-1.

**ABCD² Score**

Score points for each of the following:
- Age ≥ 60 (1)
- Blood pressure ≥ 140/90 on initial evaluation (1)
- Clinical:
  - Focal weakness (2)
  - Speech impairment without weakness (1)
- Duration
  - ≥ 60 min (2)
  - 10-59 min (1)
- Diabetes (1)

Final Score 0-7

**ABCD² Score and Stroke Risks**

*Figure: Short-term risk of stroke by ABCD² score in six groups combined (n=4799)*

SOCRATES

• Patients with minor stroke are also eligible

• NIHSS $\leq 5$

• Persisted symptoms at randomization, or positive CT or MRI stroke findings

• Must be randomized to ASA or Ticagrelor within 24 hours of stroke onset
SWIFT PRIME Neuro-Intervention

- Selecting patients with large vessel (ICA or M1) occlusion per CTA

- New generation Covidien’s Solitaire stent

- Comparing patients received IV tPa with patients getting IV tPA and mechanical embolectomy using Solitaire stent 3 months post stroke outcome
SWIFT PRIME Neuro-Intervention

- Age 18-80
- IV tPA within 4.5 hours of stroke onset
- Groin puncture within 6 hours of stroke onset or 1.5 hours after CTA (whichever earlier)
- NIHSS 8-29
Conclusions

• Novel Antiplatelet Agent – Ticagrelor for mild stroke/TIA
  – SOCRATES
• Prevention of Major Disability with Mild Stroke
  – Genentech Mild Stroke tPA trial, PRISMS
• Patients can be enrolled up to 24 hours after stroke onset
• IV tPA with neuro-intervention, SWIFT PRIME
• OPPORTUNITY for treatment modalities not yet available in general practice
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• SAFETY is always the first priority
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