Hemorrhagic Stroke in Asian Patients

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Selected slides courtesy of:
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Dr. Stephan Mayer, PI-rVIIA phase IIa ICH study

Disclosures
Research Support: NIH/NINDS, Novo Nordisk
Consulting: Astra Zeneca, Novo Nordisk, Innercool Therapies, Medivance
Stock options: Cardium Therapeutics (Innercool Therapies)

Hemorrhagic Stroke - High Burden of Disease

- High morbidity and mortality
  - 35-52% 30-day mortality
  - 20% of ICH patients independent at 6 mo
- 34% of years of potential life lost to stroke
- Lifetime cost per case ~ $124,000
- Total lifetime cost for annual US cases >$4B

Frequency of Stroke by Etiologic Subtype

Ischemic

- Thrombotic: 53%
- Embolic: 31%

Hemorrhagic

- 16%

ICH

- Intracerebral: 10%
- Subarachnoid: 6%

SAH

- 5-10% of all strokes
- Incidence: 5-16 per 100,000/ year
- Aggregate costs of $5 billion/ year
- One-third of potential years of life lost before age 65 due to stroke

Taylor et al. Stroke 26:1459-1466, 1996
ICH - Etiologies

- **Primary**
  - Hypertension (~70%)
  - Vascular malformation
    - AVM
    - Aneurysm
  - Amyloid angioathy
  - Coagulopathy
  - Sympathomimetic drugs
  - Vasculitis
  - Moya-Moya

- **Secondary**
  - Into Infarct
    - Arterial
    - Venous
  - Into Tumor

ICH - Management

- Evidenced-based vs. “In My Experience”
- No approved treatment (medical or surgical) proven beneficial in improving outcome (mortality or function) in randomized, controlled trial
- Primary and Secondary Brain Injury

ICH – Outcome Predictors

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supratentorial only (n=122)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCS</td>
<td>0.69 (0.50-0.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (≥ 65 y)</td>
<td>9.55 (2.40-38.07)</td>
<td>0.001</td>
</tr>
<tr>
<td>ICH Volume</td>
<td>1.40 (1.06-1.84)</td>
<td>0.017</td>
</tr>
<tr>
<td>Infratentorial only (n=30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCS</td>
<td>0.64 (0.46-0.88)</td>
<td>0.007</td>
</tr>
<tr>
<td>IVH</td>
<td>10.52 (6.84-131.19)</td>
<td>0.007</td>
</tr>
<tr>
<td>All ICH Patients (n=152)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCS</td>
<td>0.69 (0.50-0.80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (≥ 65 y)</td>
<td>9.84 (2.58-37.47)</td>
<td>0.001</td>
</tr>
<tr>
<td>Infratentorial Origin</td>
<td>4.24 (1.19-15.68)</td>
<td>0.030</td>
</tr>
<tr>
<td>IVH</td>
<td>2.97 (0.99-8.92)</td>
<td>0.052</td>
</tr>
<tr>
<td>ICH Volume</td>
<td>1.31 (1.00-1.71)</td>
<td>0.047</td>
</tr>
</tbody>
</table>

Odds ratio is expressed per point on the GCS score and per 10 cc of ICH Volume

Kothari et al. Stroke 27:1304-1305, 1996

ICH Volume

\[
\frac{A \times B \times C}{2}
\]

Select CT slice with largest ICH
A = longest axis (cm)
B = longest axis perpendicular to A (cm)
C = # of slices x slice thickness (cm)

Estimated volume of spheroid
Correlates well w/ planimetric CT analysis

Hemphill, Stroke 2001
**Issues in Acute ICH Treatment**

- Surgical hematoma evacuation
- Preventing hematoma enlargement
  - Hemostatic agents (recombinant factor VIIa)
- Coagulopathy-related ICH
- Blood Pressure Management

**Surgical Trial for ICH (STICH)**

- Completed in 2003
- Largest study of surgery in ICH (>1000 pts)
- Does a policy of “Early Surgery” improve outcome in patients with spontaneous supratentorial ICH compared with a policy of “Initial Conservative Treatment”?  
  - Randomisation within 72 hours of ictus
  - Surgery within 24 hours of randomisation
  - Selection based on “uncertainty principle”

**STICH Randomisation by Country**

<table>
<thead>
<tr>
<th>Country</th>
<th>No. Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>1</td>
</tr>
<tr>
<td>Austria</td>
<td>1</td>
</tr>
<tr>
<td>Belgium</td>
<td>1</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>1</td>
</tr>
<tr>
<td>Denmark</td>
<td>2</td>
</tr>
<tr>
<td>Greece</td>
<td>1</td>
</tr>
<tr>
<td>Hungary</td>
<td>1</td>
</tr>
<tr>
<td>Ireland</td>
<td>1</td>
</tr>
<tr>
<td>Italy</td>
<td>1</td>
</tr>
<tr>
<td>Japan</td>
<td>1</td>
</tr>
<tr>
<td>Latvia</td>
<td>1</td>
</tr>
<tr>
<td>Lithuania</td>
<td>1</td>
</tr>
<tr>
<td>Malaysia</td>
<td>1</td>
</tr>
<tr>
<td>Netherlands</td>
<td>2</td>
</tr>
<tr>
<td>Norway</td>
<td>1</td>
</tr>
<tr>
<td>Portugal</td>
<td>1</td>
</tr>
<tr>
<td>Singapore</td>
<td>1</td>
</tr>
<tr>
<td>South Africa</td>
<td>1</td>
</tr>
<tr>
<td>Spain</td>
<td>1</td>
</tr>
<tr>
<td>Sweden</td>
<td>1</td>
</tr>
<tr>
<td>Switzerland</td>
<td>1</td>
</tr>
<tr>
<td>Turkey</td>
<td>1</td>
</tr>
<tr>
<td>USA</td>
<td>1</td>
</tr>
</tbody>
</table>

**STICH - Results**

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Early Surgery</th>
<th>Initial Conservative tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive</td>
<td>354 (64%)</td>
<td>316 (65%)</td>
</tr>
<tr>
<td>Dead</td>
<td>171 (36%)</td>
<td>189 (37%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>Early Surgery</th>
<th>Initial Conservative tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favourable</td>
<td>112 (36%)</td>
<td>118 (24%)</td>
</tr>
<tr>
<td>Unfavourable</td>
<td>346 (74%)</td>
<td>381 (76%)</td>
</tr>
</tbody>
</table>

P=0.71  P=0.41

- No Difference
- 26% of patients randomised to Initial Conservative Treatment later had surgery
- Early surgery is not harmful
- There is no evidence favoring early surgery in supratentorial ICH

Mendelow Lancet, 2005
Hematoma Expansion in ICH

- Previously suggested as rare, suggestive of underlying AVM, coagulopathy

- Studies of early serial CT show as common
  - Fujii (1994) - 60 of 419 pts (14%)
  - Kazui (1996) – 20% w/ enlargement by 13 cc or 40%
  - Brott (1997) – 38% of 103 pts in first 20 hours

Kazui et al. Stroke 27:1783, 1996
Brott et al. Stroke 28:1, 1997

Conclusions

- **rFVIIa for acute ICH**
  - Significantly reduces hematoma growth in a dose-dependent fashion
  - Reduces mortality and significantly improves global functional outcome (mRS and BI) at 90 days
  - Is associated with a small increase in the risk of acute thromboembolic events (2% v. 7%)
FAST Trial

- Phase III Trial of rFVIIa in acute ICH
- FAST trial under way globally since May 2005; completed in November 2006
  - >120 global sites; ~70 US sites; > 10% of patients enrolled in China
  - 841 patients randomized; 821 patients dosed
- Largest ICH medical trial ever conducted
- Protocol similar to phase IIb trial
- rFVIIa 80 µg/kg vs 20 µg/kg vs placebo

FAST: Primary Results

Hematoma Growth at 24 hrs

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>20 µg/kg</th>
<th>80 µg/kg</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean % change</td>
<td>26%</td>
<td>18%</td>
<td>11%</td>
<td>0.0004</td>
</tr>
<tr>
<td>Absolute difference</td>
<td>7.8 ± 18.7</td>
<td>4.7 ± 14.8</td>
<td>3.8 ± 15.3</td>
<td>0.009 (20 µg/kg vs placebo)</td>
</tr>
</tbody>
</table>

- Dramatic effect on reducing hematoma expansion
  - similar to phase IIb study

FAST: Primary Results

<table>
<thead>
<tr>
<th>Clinical Outcome at 90 days</th>
<th>Placebo</th>
<th>20 µg/kg</th>
<th>80 µg/kg</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Rankin Score ≥ 6</td>
<td>24%</td>
<td>26%</td>
<td>29%</td>
<td>NS</td>
</tr>
<tr>
<td>Mortality</td>
<td>19%</td>
<td>18%</td>
<td>21%</td>
<td>NS</td>
</tr>
</tbody>
</table>

- Clinical outcome not affected by treatment
  - Different than phase IIb study

Warfarin-related hemorrhage

- 64 yo woman with atrial fibrillation, hypertension
  - On warfarin, INR 4.5
- FFP ordered stat, thawed and infusion initiated, INR rechecked periodically

Mayer SA. Presented at the American Academy of Neurology 59th Annual Meeting; April 28-May 5, 2007; Boston, Massachusetts.
Reversal of Anticoagulation

- Principle – any ICH in patient on warfarin (with INR > 1.4) should be considered “life-threatening”
- Goal – normal INR ASAP
- Guidelines from US, UK, Australasia recommend
  - Prothrombin complex concentrate (PCC)
  - Vitamin K (1 mg IV or 10 mg SQ)
- Less hematoma growth with PCC, with no difference with FFP if INR corrected w/in 2 hours (Huttner, Stroke 2006)
- However, PCC underutilized – lack of availability
- Reports of recombinant factor VIIa usage

BP in ICH - Expert Consensus

- Guidelines for the Management of Spontaneous Intracerebral Hemorrhage
  – AHA Stroke Council, 1999
- Blood Pressure
  - Maintain MAP < 130 mm Hg (~180/110), in patients with a h/o hypertension
  - CPP > 70 mmHg (if ICP monitoring done)
  - MAP < 100 mmHg post-op (if surgical evacuation)
  - Keep SBP > 90 mmHg

BP Lowering Trials in ICH

- INTERACT – Australia/NZ, China, probably US
  - Randomized open-label study
  - Entry criteria
    - 2 SBP measurements (≥150 to ≤300 mm Hg)
    - BP-lowering regimen < 6 h of onset
    - BP Rx goals – SBP ≤ 180 v. SBP ≤ 140
  - Primary outcome
    - Mortality and mRS (> 2) at 3m
  - 2nd outcome
    - Neurological deterioration ≤ 72h
    - Hematoma expansion at 24h and 72h
- ATACH – NIH
  - PI – Adnan Qureshi
  - “Dose-escalation” study of feasibility of achieving 3 successive BP goals for 24 hours after acute ICH
  - Safety evaluation by decrease in GCS of 2 points or NIHSS of 4 points
  - Total – 60 patients

Aneurysmal Subarachnoid Hemorrhage

- Risk factors for aneurysms/SAH
  - Female
  - Smoking
  - Hypertension
  - EtOH consumption?
Aneurysmal Subarachnoid Hemorrhage

Neurologic Complications after SAH

- Hydrocephalus
- Rebleeding
- Vasospasm
- Hyponatremia

Days

Aneurysm Treatment

- “Preventive medicine”
- Allows aggressive treatment for vasospasm

Options
- “Clipping versus coiling”
- ISAT – International Subarachnoid Aneurysm Trial
  - Lancet, 2002
  - 2143 patients
  - One-year dead/dependent
    - Clipping 30.6%
    - Coiling 23.7% (p=0.0019)

Vasospasm

36 yo woman with L carotid-ophthalmic artery aneurysm, SAH, & vasospasm

SAH D8: Mild fluctuating right hemiparesis, no aphasia, on maximal HTN therapy
**Vasospasm**

- Classical Approaches
  - Nimodipine prevents sequelae but not angiographic vasospasm
  - “triple-H” therapy (hypertension, hypervolemia, hemodilution)

- New Approaches
  - Angioplasty
  - Statins decrease inflammatory response? Clinical trials
  - Endothelin receptor antagonists – clinical trials


**Angioplasty for Vasospasm**

**Hemorrhagic Stroke**

- Is hemorrhagic stroke different across different race/ethnicities?
  - Incidence?
  - Etiology?
  - Outcome?
  - ICH or SAH or both?

**Annual Incidence of First ICH (by Age, Sex, Race)**

Greater Cincinnati/Northern Kentucky Stroke Study: 1993-1994

Usually presented as evidence of health-care disparities and generally attributed to access to health care and differential treatment of hypertension

Cerebrovascular Disease in Asia

- China
  - Stroke is more common cause of death than CAD
  - 1990 (death rate / 100,000 – males only)
    - MB Stroke
      - China 22.7 126.4
      - US 106.8 46.8
    - Hemorrhagic stroke (principally ICH) accounts for ~30% of strokes
- Japan
  - Higher incidence of aneurysmal SAH
- India
  - Single center registry, ~50% of hospital admitted stroke patients had ICH (Banerjee, J Indian Med Assoc. 2005)

Is this an “Asian Effect?”

  - 128,934 persons – self-classified ethnicity
    - 60% white, 27% black
    - 5% Chinese, 1% Japanese, 0.5% Filipino, 0.5% South Asian, 0.7% other Asian, 2.2% Mixed/Other
    - 431 with ICH (69%) or SAH (31%)
- Compared to whites
  - Increased relative risk (1.6) of hemorrhagic stroke in Asians
  - Due to increased SAH risk in Japanese (RR=3.9) and ICH risk in Filipinos (RR=2.6)
  - Adjusted for age, smoking, BP

Asians in America?

<table>
<thead>
<tr>
<th>Table II</th>
<th>Age-Adjusted Annual Death Rates (1/100,000) for Chinese and Whites in New York City, 1988–1995, and Urban Chinese in China, 1990</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chinese</td>
</tr>
<tr>
<td></td>
<td>NYC</td>
</tr>
<tr>
<td>Male</td>
<td>All causes</td>
</tr>
<tr>
<td></td>
<td>CVD (ICD 390–459)</td>
</tr>
<tr>
<td></td>
<td>Stroke (ICD 430–438)</td>
</tr>
<tr>
<td></td>
<td>CHD (ICD 410-444)</td>
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<tr>
<td></td>
<td>HT (ICD 401–405)</td>
</tr>
<tr>
<td>Female</td>
<td>All causes</td>
</tr>
<tr>
<td></td>
<td>CVD (ICD 390–459)</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>


Asians in America?

<table>
<thead>
<tr>
<th>Table IV</th>
<th>Age-Adjusted Mortality Rates for Stroke Among New York City Chinese and Whites</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NYW Whites</td>
</tr>
<tr>
<td>Male</td>
<td>Hemorrhagic stroke</td>
</tr>
<tr>
<td></td>
<td>Ischemic stroke</td>
</tr>
<tr>
<td>Female</td>
<td>Hemorrhagic stroke</td>
</tr>
<tr>
<td></td>
<td>Ischemic stroke</td>
</tr>
</tbody>
</table>

Defining Race/Ethnicity


Definitions per US Census
Race – White, Black, American Indian, API
Ethnicity – Hispanic or non-Hispanic

<table>
<thead>
<tr>
<th>TABLE 1.</th>
<th>Age standardized death rates per 100,000 population from stroke subtypes and risk factors and 95% confidence intervals comparing rates in racial/ethnic populations with those in White populations among adults aged 25 years or older, United States, 1995-1998</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Increase in rate</td>
</tr>
<tr>
<td>Stroke subtype</td>
<td>Risk factor</td>
</tr>
<tr>
<td></td>
<td>(rate/100,000)</td>
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</tbody>
</table>

* Risk ratio increases the rate for a non-Hispanic minority population with the rate for the White population.

Does this help with understanding
- Minority access to health care in US?
- Genetic predisposition to disease?
- Neither?
- Does it Matter?

No Increased Risk in Hispanics?

- Stroke subtype comparison between RMH (Buenos Aires, Argentina) and BIMC (Boston)

<table>
<thead>
<tr>
<th>TABLE 2. Stroke Subtypes in the RMH and BIMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke subtype</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Ischemic stroke</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
</tr>
<tr>
<td>Extracerebral</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
</tr>
</tbody>
</table>

* Hypertension present in 75% (RMH) and 65% (BIMC)

Saposnik, Stroke 2000

Genetic Predisposition to ICH

- Factor XIII A-subunit gene (FXIII Val34Leu) is risk factor for primary ICH
- FXIII Val34Leu present in
  - ~50% of Westerners
  - 2.5% of Asians
  - Case-control (58/48) study
  - No mutations found -> thus, no association w/ ICH
Genetics and Aneurysms

- Multiple gene loci implicated
  - Chromosome 19q13.3 as susceptibility locus
- High incidence in Japanese
  - ~2-3% with cerebral aneurysms
- Dutch MRI screening study (NEJM 2007)
  - 1.8% with incidental cerebral aneurysms

Moyamoya

- Obliterative arteropathy with b/t distal intracranial ICA occlusions or high-grade stenoses
- Usually diagnosed angiographically ("vague or hazy puff of smoke")
- More common in Asians
- Non-inflammatory with intimal thickening and smooth muscle proliferation

What About Risk Factors?

Prevalence and Magnitude of Classical Risk Factors for Stroke in a Cohort of 5092 Chinese Steelworkers Over 13.5 Years of Follow-up

- 31% prevalence of hypertension (BP > 140/90)
- Risk ratio no different for stroke among Chinese than Framingham & Honolulu for cholesterol, smoking, obesity
- Attributable risk for hypertension much higher than in whites
  - Ischemic stroke 31% v. 25%
  - Hemorrhagic stroke 42% v. 34%
- Conclusion – hypertension is a greater risk factor for stroke in Asians than whites
  - Interaction between genetics and risk factor?

Warfarin-related ICH

- Kaiser NorCal cohort
- 173 ICH events over 3.3 years
- Hazard ratio for ICH (c/w whites)
  - Asians 4.06 (2.47-6.65)
  - Hispanics 2.06 (1.31-3.24)
  - Blacks 2.04 (1.25-3.35)
- INR > 3.5 at time of ICH in 32% of Asians (c/w 11% of whites)
Warfarin for Atrial Fibrillation

- Pooled analysis of 5 primary stroke trials
  - Stroke rate (annual)
    - Non-warfarin: 4.5%
    - Warfarin: 1.4%
    - 68% risk reduction with warfarin
    - Absolute increase in major bleeding of 0.3%/year
- Shen et al. – Kaiser study
  - Annual ICH rate for Asians
    - Not on warfarin: 0.12%
    - On warfarin: 1.75%
- Bottom line – potential risk of ICH in Asians more than offset by benefit of warfarin
- Attention to level of anticoagulation is extremely important

Genetics of Warfarin Dosing

- Genotypes determine warfarin dose needs
  - Cytochrome P450 isoform CYP2CP
  - Vitamin K epoxide reductase subunit 1 VKORC1
- Couma-Gen study (Circulation 2007)
  - Randomized trial of dosing based on genotype
  - 206 subjects (95% white)
  - No difference in “within range” INRs
  - Proof of principle

Study Challenges

- Case ascertainment and quality of databases in large countries with rural populations
- Bias related to hospitalized patients
- Definitions of race/ethnicity
  - Purpose driven v. science driven
- Changing risk factors with immigration
  - Acculturation
  - Changes in diet
- Homogeneity of cohorts (White, Chinese, etc.)

UCSF ICH Cohort

<table>
<thead>
<tr>
<th>UCSF ICH Cohort (n=243)</th>
<th>San Francisco Census</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian or Alaskan Native</td>
<td>0.80%</td>
</tr>
<tr>
<td>Asian</td>
<td>44%</td>
</tr>
<tr>
<td>Black or African American</td>
<td>17.70%</td>
</tr>
<tr>
<td>Native Hawaiian or Pacific Islander</td>
<td>3.70%</td>
</tr>
<tr>
<td>White</td>
<td>33.70%</td>
</tr>
<tr>
<td>Hispanic (ethnicity)</td>
<td>5.80%</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>American Indian and Alaska Native</td>
<td>0.4%</td>
</tr>
<tr>
<td>Asian</td>
<td>30.8%</td>
</tr>
<tr>
<td>Black or African American</td>
<td>7.8%</td>
</tr>
<tr>
<td>Native Hawaiian and Other Pacific Islander</td>
<td>0.5%</td>
</tr>
<tr>
<td>White persons</td>
<td>49.7%</td>
</tr>
<tr>
<td>Persons reporting some other race</td>
<td>6.5%</td>
</tr>
<tr>
<td>Persons reporting two or more races</td>
<td>4.3%</td>
</tr>
<tr>
<td>Persons of Hispanic or Latino origin</td>
<td>14.1%</td>
</tr>
</tbody>
</table>
Summary: Hemorrhagic Stroke in Asians

- Stroke is a major cardiovascular issue in Asian patients
  - Hemorrhagic stroke accounts for a larger proportion of strokes
- Primary genetic component is possible but unclear at present
- May have increased susceptibility to modifiable risk factors
  - Hypertension
  - Anticoagulation
- Reasonable approach
  - Avoid fatalism – treat risk factors aggressively!!
  - Well-designed studies that account for
    - Genetics v. self-description
    - Include diverse cohort