Outcomes in Pediatric Stroke
Are we there yet?

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Disclosure

- I have no relevant financial relationships with the manufacture of any commercial products and/or providers of commercial products discussed in this presentation.

- I do not intend to discuss unapproved investigative use of a commercial product/device in my presentation…..but nothing is approved in children. I will discuss the use of aspirin and heparin and endovascular devices without reference to trade names or specific brands, formulations, or products.

- My wife was given 10 shares of Starbucks by her father. I will try and keep you awake, but perhaps you would enjoy a refreshing caffeinated beverage…….
**Required Disclosure Slide**

- **Requirement of Learner**
  - Participants requesting continuing education contact hours or a certificate of attendance must
    1. register for the event,
    2. attend the entire session, and
    3. complete evaluation before leaving the conference.

- **Commercial Support**
  - This educational activity received no commercial support.

- **Disclosure of Financial Conflict of Interest**
  - The speaker and planning committee have no relevant financial relationships to disclose.

- **Off Label Use**
  - I will discuss off label use of aspirin and heparin and endovascular devices in children as nothing is approved in children.

- **Non-Endorsement Statement**
  - Accredited status does not imply endorsement by Department of State Health Services - Continuing Education Services, Texas Medical Association, or American Nurses Credentialing Center of any commercial products displayed in conjunction with an activity.
Impact of Pediatric Stroke

- As common as brain tumors or leukemia

- One of the top causes of death
  - Age 1-4  Ranked 11th
  - Age 5-9  Ranked 10th
  - Age 10-14 Ranked 8th
  - Age 15-19 Ranked 10th

- Incidence 3-15/100,000/year

- As common as childhood cancers, yet limited clinical guidelines and systematic research and no randomized clinical trials for intervention or prevention
Incidence of Stroke is Increasing

- Increased awareness and reporting
- Improvement in radiographic diagnosis
- Increasing survival in previously lethal diseases that predispose to stroke
  - Congenital heart disease
  - Leukemia
  - Prematurity
  - Sickle Cell Disease
Different Strokes in Little Folks

- Presentation in children is more subtle
  - Wide differential diagnosis
  - Seizures and Headaches are more prevalent

- Risk Factors are different from adults
  - Risk factors are multiple, age-related, and poorly understood
  - Congenital heart disease, coagulopathies, vascular abnormalities in children
  - Adult RFs; atherosclerosis, A-fib, HTN, DM are rare
  - Adults have targeted approach to prevention and treatment

- Coagulation, vascular, and neurological systems differ
Different Strokes in Little Folks

- Cannot predict or prevent with lifestyle changes

- No “established” treatments in children

New Measures
- PedNIH Stroke Scale
- PSOM: Pediatric Stroke Outcome Measure
- RRQ: Recovery and Recurrence Questionnaire
- Classification: TOAST is toast…CASCADE
  - Childhood AIS Standardized Classification And Diagnostic Evaluation

Better Outcomes

International Pediatric Stroke Study

- Started January 2003
- 302 investigators

- 199 centers
  - (75 enrolling)

- 45 countries

- As of 2015
  - Data lock
  - n = 4267
  - UTSW = 225
Are We There Yet? What to “Measure”

- Are we recognizing stroke in children in the ER?
  - Screening Tools
- How much evidence is in our “Evidence Based Guidelines”?
- What is an adequate/complete diagnostic evaluation?
- Are we “ready” for Performance Measures?
- How effectively are we treating?

- Short-term outcome measures
- Long-term clinical outcomes
Are We There Yet?  Stroke Recognition

- 3 yo boy with history of complex congenital heart disease
  - Single ventricle physiology
  - 1 month s/p palliative surgery with fenestrated Fontan

- Fell to the floor while playing and could not move left arm or leg and he was drooling from the left side of his mouth

- Taken to outside hospital
  - Radiographs of left arm and leg were normal
  - Discharged home with splint

- 8 hours later mother brought him to CMC ERC
Are We There Yet?  Stroke Recognition

- MRI showed R MCA infarct
- MRA with absence of flow in R M1 segment of MCA
- Cardiac MRI showed thrombus in the Fontan pathway
5 More Cases Like This

We’re not there yet......
Missing the Diagnosis

- > 60% of children with acute stroke: diagnosis is delayed
  - > 12 hours after onset (to adult tertiary ER)
  - > 24 hours after onset (to pediatric tertiary ER)

- 10% of children with AIS have had a “missed” prior stroke or TIA

*data from the Canadian Pediatric Ischemic Stroke Registry*
Points

- Education of Physicians/Nurses/EMT
  - Stroke Recognition
- Education of Parents of High Risk Groups
  - Stroke Recognition
  - Stroke Medic-Alert in
    - High Risk Cardiac Patients?
    - SCD?
    - Moyamoya?
In adults, multiple screening tools predict presence of stroke with reasonable sensitivity and specificity.

They don’t work in children:
- Case/Control Study of an adult stroke tool in childhood AIS
  - COTS (Central Ohio Trauma System) screening tool
    - Dec LOC, slurred speech, facial droop, arm drift
  - 58 children with AIS
  - 57 Controls with Bells palsy or acute hemiparesis
  - COTS stroke scale was NOT DIFFERENT between AIS and controls

Gramling and Lo, CNS abst160, 2014
Screening Tools

- In adults, multiple screening tools predict presence of stroke with reasonable sensitivity and specificity.

- They don’t work in children.
  - Case/Control Study of an adult stroke tool in childhood AIS
    - COTS (Central Ohio Trauma System) screening tool
      - Dec LOC, slurred speech, facial droop, arm drift
    - 58 children with AIS
    - 57 Controls with Bells palsy or acute hemiparesis
    - COTS stroke scale was NOT DIFFERENT between AIS and controls

- But, what do we want to measure with the scale?
  - Stroke or need for a stat MRI?

Gramling and Lo, CNS abst160, 2014
CMC Acute Stroke Team  5 Year Summary

361 AST calls/334 pts

- Stroke (41%)
- TIA (14%)
- Seizure (13%)
- Migraine (9%)
- Conversion (2%)
- Meth/PRES (5%)
- Trauma (2%)
- Tumor (2%)
- Other (9%)
- Unknown (2%)
Screening Tools

- With a high prevalence of stroke mimics in children, what do we want the screening tool to measure?
  - Stroke?
  - "Actionable MRI finding"?

- We may want to measure "need" for that urgent MRI at 2:00AM
  - ADEM
  - PRES/methotrexate
  - Tumors
  - Trauma

- Neuroradiology happy with our false alarm rate
Points

- Education of Physicians/Nurses/EMT/High Risk Groups

Screening Tools to Screen for what?

- Stroke?
- Pretty good reason to get stat MRI?
Are we ready to “Get with the Guidelines”?
Published Guidelines

- American Heart Association

- American College of Chest Physicians
Guidelines Are the Experts there yet?

How good are the guidelines?

Roach Stroke Guidelines: Of 93 recommendations

- Only 2 graded level of evidence “A”
  - Transfusion for children with SCD and abnormal TCD
  - Provide factor replacement for children with factor deficiency

- 17 are “level B” evidence from single or non-randomized trials

- Rest are “level C” from expert opinion, case studies or standard of care
Points

- Education of Physicians/Nurses/EMT/High risk patients
- Screening Tools to Screen for what?
- Evidence Based Guidelines need Evidence
Can we use the Adult “Stroke Performance Measures”
AHA/ASA Performance Measures for AIS

- Venous thromboembolism prophylaxis
- Discharged on antithrombotic therapy
- Anticoagulation therapy for atrial fibrillation/flutter
- Thrombolytic therapy
- Antithrombotic therapy by end of hospital day 2
- Discharged on statin medication
- Stroke education
- Tobacco use counseling
- Assessed for rehabilitation
- Time to intravenous thrombolytic therapy
- Dysphagia screen: assessment
- Dysphagia screen: management
- NIHSS assessment
- Cardiac monitoring
- Early carotid imaging

These measures specifically exclude patients < 18 years old!

Smith, et al., Stroke, 2014
Development of Pediatric Stroke Centers: TIPS 2003-2013

- >3 Subspecialists dedicated to stroke
- Pediatric stroke neurologist
- MRI stroke availability 24/7
- Stroke team
- Sedated MRI stroke availability 24/7
- Stroke ED orderset
- Stroke ICU orderset
Points

- Education of Physicians/Nurses/EMT/High risk patients
- Screening Tools to Screen for what?
- Evidence Based Guidelines need Evidence
- It's time for some **Pediatric** Stroke Performance Measures
Etiologies of Stroke in Children
A Perfect Storm
Stroke Evaluation: Do we have to do everything?

- In the IPSS, even without systematic evaluation 50% had 2 or more risk factors
- Does childhood AIS represent a “perfect storm” with multiple RFs contributing to stroke?
  - Does every patient need every test?
  - Full hypercoag eval?
  - Echocardiogram?
  - Vascular Imaging?
- What about SCD?
Oliver

11 y.o. with Hgb SS presented with severe HA following transfusion for aplastic crisis. Severe HA recurred on Day 3 Neuro Examination normal. No vasculopathy

PFO identified

Elevated α-phospholipid Ab
Lipoprotein a
Factor VIII

Dowling, et al., 2009
Potential R-to-L Shunting in SCD patients with Stroke vs Controls

<table>
<thead>
<tr>
<th></th>
<th>SCD/Stroke (n=153)</th>
<th>Control (n=129)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shunting Detected</td>
<td>43.1%</td>
<td>20.0%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- Increased prevalence of potential right-to-left shunting in SCD/stroke patients compared to non-SCD non-stroke controls
- Contrasted echocardiogram
- Any Intracardiac or Intrapulmonary shunting (“late bubbles”)

Intracardiac or Intrapulmonary shunting ("late bubbles")
Points

- Education of Physicians/Nurses/EMT/High risk patients
- Screening Tools to Screen for what?
- Evidence Based Guidelines need Evidence
- Need Pediatric Stroke Performance Measures

**Everybody may need Everything Evaluated**
- Or maybe everybody might need MORE
- Multiplicity of RF… “perfect storm”
Are Outcomes Better in Children than Adults?
Case

- 16 yo M
- Wrestling
- Unsteady
- Unable to walk
- Vertebral and basilar arteries absent
After tPA and clot extraction
Reconstitution of posterior circulation
- Pontine infarct
- Locked-in syndrome
Posterior circulation stroke survival and outcomes are better in children than adults in several series.
Outcomes in Pediatric Stroke Trials

- Death
  - Easy but hopefully rare
- Bleed/hemorrhagic transformation
- Recurrence
  - Silent/overt/extension
  - Early/late
- Clinical Outcome measures: Motor, sensory, language, cognitive
- Functional abilities
- Long term outcomes
- QOL: Quality of life

- Safety?
- Cost?
Neurological Status at Discharge - AIS
N = 1113

Neonate N = 335  Older N = 778

<table>
<thead>
<tr>
<th>Category</th>
<th>Neonate (&lt; or equal to 28 days of life)</th>
<th>Older infant or child</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2.4%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Neurologic Deficit</td>
<td>37.3%</td>
<td>67.1%</td>
</tr>
<tr>
<td>Normal</td>
<td>46.3%</td>
<td>19.4%</td>
</tr>
<tr>
<td>Unknown</td>
<td>14.0%</td>
<td>9.9%</td>
</tr>
</tbody>
</table>
Short Term Outcomes

- How important is early recurrence or extension?
  - 27/54 (50%) of patients with AIS had infarct recurrence or extension on routine f/u MRI at <2w
  - Most were clinically silent or difficult to determine in children
  - Per CMC protocol, all pts w/o contraindication are Rx with heparin

- Can early recurrence/extension on MRI be used as early outcome measure for trials?

- Do we need more intense treatment?
  - ASA plus Heparin if 50% are having early recurrence or extension?
Huge variety of measures used! **38 measures used in 34 Studies.**

Mean 2 measures per study. Study outcomes not comparable….

Standard Pediatric Outcome Measures

- Pediatric Stroke Outcome Measure
  - The only validated outcome measure in pediatric stroke
- Standardized Neuro Exam
  - Range: 0 to 10; 0 is best

- PSOM = 5 subscores:
  - Sensorimotor right
  - Sensorimotor left
  - Language Deficit - Production
  - Language Deficit - Comprehension
  - Cognition/Behavior

- Each subscore assigned:
  - 0 (no deficit)
  - 0.5 (mild/no impact on fxn)
  - 1 (moderate w some limited fxn)
  - 2 (severe/profound)

- Many other measures utilized:
  - Developmental Scales
  - Intelligence tests
  - Pediatric Evaluation of Disability Inventory (“Ped Barthel”)
  - mRS
  - KOSCHI

Kitchen, et al., PSOM: A Validation and Reliability Study; Stroke 2012
Outcome Measure Challenges

- Children grow and develop
  - Stroke can change developmental trajectory
- We need outcomes from when children are no longer under our care
  - College?
  - Employment?
  - Family?
  - Will this child be able to live independently?
- Preexisting Deficits in our high risk AIS population
  - Congenital heart disease
  - Cancer
  - Genetic syndromes (Downs)
What if they don’t come back?

- Recurrence and Recovery Questionnaire (RRQ)
  - PSOM converted for telephone interview
  - Validated in a cohort of 232 children with AIS or CSVT and same day neurologist performed PSOM and parents RRQ responses
  - RRQ was a reliable estimator of PSOM total & components
  - Chronic illness effect: increased difference between total PSOM and RRQ scores.
  - RRQ can be used when child cannot return for examination in long-term follow up studies

Lo, et al., Neurology, 2012
Problem

- What’s a good outcome?
  - PSOM ≥ 1 = poor outcome?
  - Does it depend on your starting point?
  - Locked in patient, recovers to PSOM = 2
    - 1 for motor R, 0.5 motor left, 0.5 behavioral
    - This would be classified as poor outcome
  - Berlin Heart Study used different criteria (as alternative to use of this ventricular assist device was death)
    - Unacceptable neurologic deficits
      - Comatose
      - Quadriplegia (PSOM 3-4 on motor scale)
      - Severe Global Aphasia (PSOM 3-4 on language scales)
      - Severe Cognitive deficits (PSOM 2 on cognitive scale)
  - All scales are imperfect, but need careful analysis with analysis of subcomponents
  - Mostly, we need data

Almond, et al., 2013
Tantalizing Observations from Single Center Studies

- Early or “selective vulnerability” at early ages
- Localization cortical/subcortical effects as well

Westmacott, et al., 2009

Pavlovic, et al., 2006
Tantalizing Observations from Single Center Studies

- Lesion size might be important

Everts, et al., 2008

n=21
Case A  Decompressive Hemicraniectomy
CT 1/2015
Case B  Decompressive Hemicraniectomy
CT 6/2015
6 Randomized controlled studies of DH for malignant MCA stroke (314 patients total) with Primary outcomes:

- Death
- Disability by Modified Rankin Score
  - Major disability >3
  - Severe disability >4

- mRS 0 = No symptoms
- mRS 1 = No significant disability. All usual activities ok
- mRS 2 = Slight disability...able to look after own affairs but can’t do all prior activities
- mRS 3 = moderate disability, able to walk unassisted, requires some help
- mRS 4 = moderately severe disability, unable to attend to own bodily needs without assistance and unable to walk unassisted
- mRS 5 = Severe, requires constant nursing case and attention, bedridden, incontinent
- mRS 6 = Dead

Yang, et al., 2015
## Meta-analysis of DH RCTs

### Death at 12m

### 5.1.1 Age ≤ 60 years

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DHC Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Peto Odds Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>DESTINY 2007</td>
<td>3</td>
<td>17</td>
<td>8</td>
<td>15</td>
<td>9.9%</td>
<td>0.22 [0.05, 0.91]</td>
<td>2007</td>
</tr>
<tr>
<td>DECIMAL 2007</td>
<td>5</td>
<td>20</td>
<td>14</td>
<td>18</td>
<td>13.0%</td>
<td>0.13 [0.04, 0.45]</td>
<td>2007</td>
</tr>
<tr>
<td>HAMLET 2009</td>
<td>7</td>
<td>32</td>
<td>19</td>
<td>32</td>
<td>20.9%</td>
<td>0.22 [0.08, 0.58]</td>
<td>2009</td>
</tr>
<tr>
<td>Zhao 2012</td>
<td>1</td>
<td>8</td>
<td>7</td>
<td>10</td>
<td>6.2%</td>
<td>0.11 [0.02, 0.68]</td>
<td>2012</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>77</strong></td>
<td><strong>75</strong></td>
<td><strong>50.0%</strong></td>
<td></td>
<td></td>
<td><strong>0.17 [0.09, 0.33]</strong></td>
<td></td>
</tr>
</tbody>
</table>

#### Heterogeneity:
- $\chi^2 = 0.74$, df = 3 ($P = 0.88$); $I^2 = 0$
- Test for overall effect: $Z = 5.36$ ($P < 0.00001$)

### 5.1.2 Age > 60 years

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DHC Events</th>
<th>Total</th>
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<td>Zhao 2012</td>
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<td>9</td>
<td>13</td>
<td>9.6%</td>
<td>0.13 [0.03, 0.58]</td>
<td>2012</td>
</tr>
<tr>
<td>DESTINY II 2014</td>
<td>20</td>
<td>47</td>
<td>47</td>
<td>62</td>
<td>34.1%</td>
<td>0.25 [0.11, 0.54]</td>
<td>2014</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>63</strong></td>
<td><strong>75</strong></td>
<td><strong>43.7%</strong></td>
<td></td>
<td></td>
<td><strong>0.22 [0.11, 0.43]</strong></td>
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</tr>
</tbody>
</table>

#### Heterogeneity:
- $\chi^2 = 0.54$, df = 1 ($P = 0.46$); $I^2 = 0$
- Test for overall effect: $Z = 4.37$ ($P < 0.00001$)

### 5.1.3 Unclear

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DHC Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
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<th>Peto Odds Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slazins 2012</td>
<td>6</td>
<td>11</td>
<td>12</td>
<td>13</td>
<td>6.2%</td>
<td>0.15 [0.02, 0.89]</td>
<td>2012</td>
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<td><strong>13</strong></td>
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<td></td>
<td></td>
<td><strong>0.15 [0.02, 0.89]</strong></td>
<td></td>
</tr>
</tbody>
</table>

#### Total events:
- 6

#### Heterogeneity:
- Not applicable
- Test for overall effect: $Z = 2.08$ ($P = 0.04$)

### Total (95% CI)

<table>
<thead>
<tr>
<th>DHC Events</th>
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<tbody>
<tr>
<td>151</td>
<td>163</td>
<td>100.0%</td>
<td></td>
<td></td>
<td>0.19 [0.12, 0.30]</td>
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</tbody>
</table>

#### Total events:
- 45

#### Heterogeneity:
- $\chi^2 = 1.58$, df = 6 ($P = 0.95$); $I^2 = 0$
- Test for overall effect: $Z = 7.20$ ($P < 0.00001$)
- Test for subgroup differences: $\chi^2 = 0.31$, df = 2 ($P = 0.86$); $I^2 = 0$
Meta-analysis of DH RCTs: Death or Severe Disability at 12m (mRS>4)

B

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DHC</th>
<th>Control</th>
<th>Peto Odds Ratio</th>
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<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>4.1.1 Age \leq 60 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>DECIMAL 2007</td>
<td>5</td>
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<td>14</td>
<td>18</td>
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<tr>
<td>DESTINY 2007</td>
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<td>75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>23</td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 3.73, df = 3 (P = 0.29); I² = 20%</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 4.50 (P &lt; 0.00001)</td>
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</tr>
</tbody>
</table>

| 4.1.2 Age > 60 years |           |       |        |       |         |               |      |
| Zhao 2012           | 5     | 16     | 13     | 13    | 10.7%   | 0.06 [0.01, 0.26] | 2012 |
| DESTINY II 2014     | 29    | 47     | 62     | 62    | 22.8%   | 0.06 [0.02, 0.18] | 2014 |
| Subtotal (95% CI)   | 63    | 75     |        |       | 33.5%   | 0.06 [0.03, 0.14] |      |
| Total events        | 34    | 75     |        |       |         |               |      |
| Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² = 0% |        |         |               |      |
| Test for overall effect: Z = 6.49 (P < 0.00001) |        |         |               |      |

| 4.1.3 Unclear |           |       |        |       |         |               |      |
| Slazins 2012   | 6     | 11     | 12     | 13    | 7.1%    | 0.15 [0.02, 0.89] | 2012 |
| Subtotal (95% CI) | 11    | 13     |        |       | 7.1%    | 0.15 [0.02, 0.89] |      |
| Total events   | 6     | 12     |        |       |         |               |      |
| Heterogeneity: Not applicable |        |         |               |      |
| Test for overall effect: Z = 2.08 (P = 0.04) |        |         |               |      |

Total (95% CI) | 151    | 163    | 100.0% |       | 0.15 [0.09, 0.24] |
Total events   | 63     | 137    |        |       |               |
Heterogeneity: Chi² = 9.90, df = 6 (P = 0.13); I² = 39% |        |         |               |      |
Test for overall effect: Z = 7.78 (P < 0.00001) |        |         |               |      |
Test for subarandom differences: Chi² = 6.17, df = 2 (P = 0.05). I² = 67.6% |        |         |               |      |
Meta-analysis of DH RCTs
Major Disability in survivors (mRS 4-5)

<table>
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<th>Peto Odds Ratio</th>
<th>Peto, Fixed, 95% CI</th>
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<td>1.00 [0.17, 5.98]</td>
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<td></td>
</tr>
<tr>
<td>DECIMAL 2007</td>
<td>5</td>
<td>15</td>
<td>0</td>
<td>4</td>
<td>10.4%</td>
<td>5.10 [0.45, 58.35]</td>
<td>2007</td>
<td></td>
</tr>
<tr>
<td>HAMLET 2009</td>
<td>17</td>
<td>25</td>
<td>5</td>
<td>13</td>
<td>34.4%</td>
<td>3.25 [0.85, 12.42]</td>
<td>2009</td>
<td></td>
</tr>
<tr>
<td>Zhao 2012</td>
<td>3</td>
<td>7</td>
<td>1</td>
<td>3</td>
<td>9.0%</td>
<td>1.43 [0.10, 19.61]</td>
<td>2012</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>61</td>
<td>27</td>
<td></td>
<td></td>
<td>73.0%</td>
<td>2.30 [0.92, 5.76]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>31</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 1.63$, df = 3 ($P = 0.65$); $I^2 = 0\%$
Test for overall effect: $Z = 1.77$ ($P = 0.08$)

<table>
<thead>
<tr>
<th>12.1.2 Age &gt; 60 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhao 2012</td>
</tr>
<tr>
<td>DESTINY II 2014</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
</tr>
<tr>
<td>Total events</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 1.17$, df = 1 ($P = 0.28$); $I^2 = 14\%$
Test for overall effect: $Z = 0.31$ ($P = 0.76$)

<table>
<thead>
<tr>
<th>12.1.3 Unclear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slazins 2012</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
</tr>
<tr>
<td>Total events</td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: $Z = 2.24$ ($P = 0.03$)

Total (95% CI)      | 106        | 47        | 100.0%         | 1.71 [0.78, 3.74] |
Total events         | 66         | 26        |                |                |

Heterogeneity: $\chi^2 = 9.25$, df = 6 ($P = 0.16$); $I^2 = 35\%$
Test for overall effect: $Z = 1.33$ ($P = 0.18$)
Test for subhoraous differences: $\chi^2 = 6.46$, df = 2 ($P = 0.04$). $I^2 = 69.0\%$
### Meta-analysis of DH RCTs: Death or Major Disability at 12m (mRS>3)

#### A

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DHC Events</th>
<th>DHC Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Peto Odds Ratio</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>10.1.1 Age ≤ 60 years</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>DECIMAL 2007</td>
<td>10</td>
<td>20</td>
<td>14</td>
<td>18</td>
<td>20.2%</td>
<td>0.31 [0.09, 1.15] 2007</td>
</tr>
<tr>
<td>DESTINY 2007</td>
<td>9</td>
<td>17</td>
<td>11</td>
<td>15</td>
<td>17.2%</td>
<td>0.43 [0.10, 1.77] 2007</td>
</tr>
<tr>
<td>HAMLET 2009</td>
<td>24</td>
<td>32</td>
<td>24</td>
<td>32</td>
<td>27.2%</td>
<td>1.00 [0.33, 3.07] 2009</td>
</tr>
<tr>
<td>Zhao 2012</td>
<td>4</td>
<td>8</td>
<td>8</td>
<td>10</td>
<td>9.3%</td>
<td>0.28 [0.04, 1.90] 2012</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>77</td>
<td>75</td>
<td>158</td>
<td>180</td>
<td>74.0%</td>
<td>0.51 [0.26, 1.01]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>47</td>
<td>57</td>
<td>174</td>
<td>190</td>
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<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Chi² = 2.36, df = 3 (P = 0.50); I² = 0%</td>
<td></td>
</tr>
<tr>
<td>Test for overall effect:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Z = 1.94 (P = 0.05)</td>
<td></td>
</tr>
<tr>
<td><strong>10.1.2 Age &gt; 60 years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhao 2012</td>
<td>14</td>
<td>16</td>
<td>13</td>
<td>13</td>
<td>4.3%</td>
<td>0.15 [0.01, 2.61] 2012</td>
</tr>
<tr>
<td>DESTINY II 2014</td>
<td>44</td>
<td>47</td>
<td>59</td>
<td>62</td>
<td>12.5%</td>
<td>0.75 [0.14, 3.90] 2014</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>63</td>
<td>75</td>
<td>138</td>
<td>171</td>
<td>16.8%</td>
<td>0.50 [0.12, 2.08]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>58</td>
<td>72</td>
<td>230</td>
<td>266</td>
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<tr>
<td>Heterogeneity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Chi² = 0.89, df = 1 (P = 0.34); I² = 0%</td>
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</tr>
<tr>
<td>Test for overall effect:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Z = 0.95 (P = 0.34)</td>
<td></td>
</tr>
<tr>
<td><strong>10.1.3 Unclear</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slazins 2012</td>
<td>6</td>
<td>11</td>
<td>13</td>
<td>13</td>
<td>9.2%</td>
<td>0.07 [0.01, 0.49] 2012</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>11</td>
<td>13</td>
<td>26</td>
<td>26</td>
<td>9.2%</td>
<td>0.07 [0.01, 0.49]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>6</td>
<td>13</td>
<td>39</td>
<td>39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not applicable</td>
<td></td>
</tr>
<tr>
<td>Test for overall effect:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Z = 2.67 (P = 0.007)</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>151</td>
<td>163</td>
<td>314</td>
<td>314</td>
<td>100.0%</td>
<td>0.42 [0.24, 0.76]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>111</td>
<td>142</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Chi² = 6.84, df = 6 (P = 0.34); I² = 12%</td>
<td></td>
</tr>
<tr>
<td>Test for overall effect:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Z = 2.87 (P = 0.004)</td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Chi² = 3.59, df = 2 (P = 0.17). I² = 44.3%</td>
<td></td>
</tr>
</tbody>
</table>
Would You Want One?

- Survey of healthcare workers in Nsurgery Center in Australia (n=773)
  - 53% initially would give consent for themselves
  - 18.1% unwilling to have procedure
    - Only 8.7% felt mRS≥4 was acceptable
    - 7.4% felt mRS=4 was acceptable
- After review of Outcomes data for DH
  - 37.8% unwilling
    - But more were ready to accept
      - 11.9% felt mRS≥4 was acceptable
      - 10.2% felt mRS=4 was acceptable
- So, most felt survival with dependency was unacceptable but many would consent in hope for better outcome
DH in Children

- Literature Review (Shah, et al., 2013)
  - N=26
  - None had mRS equivalent >4!
    - Bias in reporting of good outcomes
    - Even in presence of herniation, low GCS, multiple vascular territories, longer time to surgery
  - Adult prognostic factors may not apply to children
    - Age, time to surgery, infarct size, size of craniectomy, higher GCS score, just one vascular territory, and present of mydriasis
  - Complications noted: infection
Are we there yet?  No, but we are getting there

- Education of Physicians/Nurses/EMT/High risk patients
- Screening Tools to Screen for what?
- Evidence Based Guidelines need Evidence
- We need Pediatric Performance Measures
- Everybody may need Everything Evaluated
- We need to use Pedi Classification systems
- We need both short and long term outcome measures
- More extensive use of PSOM/RRQ and other measures
- Neuropsychological testing in larger multicenter cohorts
New Model Organism for Adult Stroke Research

- Similar anatomy, neurobiology, and immunology
- NO complicating disease factors
  - Diabetes, HTN, smoking, atherosclerosis
- Superior neuro-regenerative capacity
- Longer lifespan than typical stroke patient
- Willingly participate in rehabilitation programs
- No “Placement issue”
  - Each model organism usually has 2 dedicated therapists/aides
CMC Acute Stroke Team
Janna Journeycake
Nancy Rollins
Maeve Sheehan
Korgun Koral
Pam Okada
Claudio Ramacciotti
Didem Inanoglu
Peter Stavinoah
Patricia Plumb
Stefanie Beavers

International Pediatric Stroke Study
Gabrielle de Veber
Rebecca Ichord
Fenella Kirkham
Lori Jordan

Doris Duke Charitable Foundation
First American Real Estate Information Services, Inc.
Women’s Auxiliary to Children's Medical Center
After We Decide What to Measure...Analyzing Outcomes

- **Dichotomous**
  - mRS $\geq 3$ is a poor outcome, PSOM $\geq 1$ is a poor outcome
  - Dichotomizing outcome scales reduces complexity, but discards substantial outcome information such as improvement...

- **Continuous**
  - **Global Statistic** — multiple outcome measures analyzed together
  - **Responder Analysis** — adjusts for baseline severity.
  - **Shift (Rank) Analysis** — change in outcome distribution/rank
  - **Rasch Analysis** — transforming ordinal scales to interval scales
    - Ordinal change of 1 in mRS... mRS $1 \rightarrow 2$ is not the same as $5 \rightarrow 6$