Inflammatory Biomarkers in Acute Stroke and Stroke Prevention

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NINDS StrokeNet Educational Webinar
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NINDS P50 NS 49660, R01 NS 555809, R01 NS 62820,
LeDucq; diaDexus, Inc.; BMS-Sanofi Partnership

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BMS-Sanofi Partnership; BMS-Pfizer; Biogen IDEC;
Jarvik Heart; diaDexus, Inc.; Novartis/Organon; Merck;
Daiichi-Sankyo; Janssen; Boehringer-Ingelheim

Inflammatory Biomarkers in Acute Stroke and Stroke Prevention

Outline
• Inflammatory markers and stroke risk
• Infectious markers and stroke risk
• Acute infection and stroke risk
• Inflammation and acute stroke

Implications for stroke trials?

The response-to-injury hypothesis of atherosclerosis

Oxidized LDL  Homocysteine  Toxins  Mechanical forces  ?Infectious agents

Endothelial injury/dysfunction

Monocyte and T lymphocyte adhesion, diapedesis, subendothelial localization

Lipid accumulation/ Foam cell formation Macrophage activation Cytokine/GF release

Smooth muscle proliferation/Fibrous plaque formation


NOMAS
Baseline leukocyte quartile and stroke risk

Serum Markers of Inflammation Potentially Associated with Stroke and Vascular Events

- **WBC**
  - Acute Phase Proteins
    - C-reactive protein (CRP)
    - Serum amyloid A (SAA)
    - Haptoglobin
  - Cytokines
    - IL-2
    - IL-10
    - IL-6
    - IL-18
    - IL-8
    - TNF
    - TNF receptors
  - Cellular adhesion molecules
    - sICAM-1
    - VCAM
    - E-selectin

- Other
  - CD40 Ligand
  - Monocyte Chemotactant Protein-1
  - LSR
  - Lipoprotein-associated phospholipase A2

Association between leukocyte count and ischemic stroke risk


C-Reactive Protein

- Acute phase protein
- Produced in liver and endothelial cells
- Final common pathway of cytokine activation
- Produced in response to a variety of infectious and inflammatory stimuli (“non-specific”)
- Predicts incident atherosclerotic and cardiovascular events


NOMAS: HsCRP predicts MI but not stroke

Elkind MSV et al. Neurology 2009;73:1300-1307

CRP is associated with other risk factors

- **Increased CRP**
  - Hypertension
  - BMI
  - Obesity
  - Diabetes
  - Metabolic syndrome
  - Smoking
  - Hormone use

- **Decreased CRP**
  - Alcohol consumption
  - Physical activity
  - Weight loss
  - Medications
  - Statins
  - ACEI

Most studies that have shown an association between hsCRP and risk factors have been done in stroke-free subjects

PRIMARY PREVENTION:
CDC/AHA Consensus On Inflammatory Markers

1. HsCRP assay is optimal inflammatory marker thus far
2. HsCRP may be useful in estimating risk of future cardiovascular events, particularly in persons at intermediate risk based on other risk factors

<table>
<thead>
<tr>
<th>hsCRP concentration</th>
<th>Risk Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 mg/L</td>
<td>Low</td>
</tr>
<tr>
<td>1-3 mg/L</td>
<td>Medium</td>
</tr>
<tr>
<td>&gt;3 mg/L</td>
<td>High</td>
</tr>
</tbody>
</table>


Lipoprotein-associated phospholipase A2

- 50 kDa, Ca-independent lipase produced by macrophages
- Resides mainly on LDL in human plasma
- Highly upregulated in atherosclerosis
- Lp-PLA2 oxidizes LDL, generating pro-inflammatory mediators:
  - Lyso phosphatidylcholine (lyso-PC) and Oxidized fatty acid (oxFA)
- In pre-clinical animal studies, inhibition of Lp-PLA2 attenuates inflammatory process and slows atherosclerotic disease progression.

Approved by FDA for prediction of risk of first ischemic stroke.


Darapladib, an inhibitor of LpPLA2, tested in phase 3 trial

NOMAS: LpPLA2 and atherosclerotic stroke

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>Model 1*</th>
<th>Model 2**</th>
</tr>
</thead>
<tbody>
<tr>
<td>LpPLA2-mass (per SD)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Q1 (28.1-245.6)</td>
<td>1.57 (1.26-1.96)</td>
<td>1.49 (1.18-1.88)</td>
<td>1.55 (1.17-2.04)</td>
</tr>
<tr>
<td>Q2 (245.7-307.2)</td>
<td>1.34 (0.92-1.94)</td>
<td>1.15 (0.76-1.73)</td>
<td>1.17 (0.71-1.92)</td>
</tr>
<tr>
<td>LpPLA2-activity (per SD)</td>
<td>Ref.</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
<tr>
<td>Q1 (28.1-245.6)</td>
<td>Ref.</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
<tr>
<td>Q2 (245.7-307.2)</td>
<td>1.53 (0.26-6.15)</td>
<td>1.42 (0.24-8.52)</td>
<td>1.43 (0.25-8.46)</td>
</tr>
<tr>
<td>Q3 (307.2-365.5)</td>
<td>4.63 (1.09-21.44)</td>
<td>4.09 (0.88-19.12)</td>
<td>4.47 (0.93-21.54)</td>
</tr>
<tr>
<td>Q4 (365.5-972.6)</td>
<td>6.19 (1.39-27.64)</td>
<td>4.88 (1.06-22.45)</td>
<td>5.07 (1.07-24.86)</td>
</tr>
</tbody>
</table>

Model 1: adjusted age, sex, race-ethnicity, education.
Model 2: adjusted for age, sex, race-ethnicity, education, waist circumference, physical activity, moderate alcohol consumption, smoking, diabetes mellitus, systolic blood pressure, coronary artery disease, LDL, HDL.


Northern Manhattan (Stroke) Study Epidemiological Study Designs

- Incidence study
- Stroke case F/U
- Case control study
- Cross-sectional study
- Prospective cohort study
- Nested case-control

NOMAS stroke survivor follow-up:

<table>
<thead>
<tr>
<th></th>
<th>HsCRP HR (95% CI)</th>
<th>Lp-PLA2 HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent stroke (N=540 outcome events)</td>
<td>0.86 (0.45-1.65)</td>
<td>2.30 (1.21-4.36)</td>
</tr>
<tr>
<td>Unadjusted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted for demographics, risk factors, and both markers</td>
<td>0.69 (0.34-1.35)</td>
<td>2.56 (1.02-6.26)</td>
</tr>
<tr>
<td>Recurrent stroke, MI, vascular death (N=122 events)</td>
<td>1.86 (1.33-2.60)</td>
<td>2.38 (1.36-4.17)</td>
</tr>
<tr>
<td>Unadjusted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted for demographics, risk factors, stroke severity, and both markers</td>
<td>0.93 (0.54-1.61)</td>
<td>1.86 (1.01-3.42)</td>
</tr>
<tr>
<td>Death (N=158 outcome events)</td>
<td>4.50 (2.83-7.15)</td>
<td>2.29 (1.43-3.67)</td>
</tr>
<tr>
<td>Unadjusted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted for demographics, risk factors, stroke severity, and both markers</td>
<td>1.97 (1.13-3.46)</td>
<td>1.41 (0.84-2.38)</td>
</tr>
</tbody>
</table>

Demographics: age, sex, race-ethnicity. Risk factors: history of CAD, DM, HTN, hyperlipidemia, AF, and smoking.

Results: Inflammatory markers and stroke severity

![Graph showing proportion of patients in 4th quartile for HsCRP and Lp-PLA2](image)


Levels of Inflammatory Markers in the Treatment of Stroke

**LIMITS**

An ancillary prospective cohort study in patients with lacunar stroke in the SPS3 trial

**Hypotheses**

1. Elevated levels of hsCRP measured after lacunar stroke increase risk of:
   a. recurrent ischemic stroke (IS) and
   b. recurrent IS, MI, or vascular death.

2. Elevated levels of inflammatory markers predict response to dual antplatelet therapy.


NOMAS: Biomarker levels before and after acute stroke/MI

![Graph showing CRP and LpPLA2 levels](image)


**Stroke Prevention:**

The Secondary Prevention of Small Subcortical Strokes Trial (SPS3)

PI: Oscar Benavente

Univ Texas Health Sci Center, San Antonio

Lacunar stroke patients up to 6 months post stroke randomized to:

- aspirin + placebo
- aspirin + clopidogrel

Target levels of BP:
- "usual" 130-149 mmHg syst. or
- "intensive" <130 mmHg syst.

LIMITS Sites

![Map showing LIMITS Global Recruitment Map](image)


LIMITS: Risk of recurrent ischemic stroke

CDC/AHA clinical thresholds (n=1244)

<table>
<thead>
<tr>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>0.04</td>
<td>0.05</td>
<td>0.06</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>hsCRP</th>
<th>P</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1 mg/L</td>
<td>1.75</td>
<td>0.90-2.85</td>
<td>1.72</td>
</tr>
<tr>
<td>1-3 mg/L</td>
<td>2.10</td>
<td>1.15-3.84</td>
<td>2.22</td>
</tr>
<tr>
<td>&gt;3 mg/L</td>
<td>2.22</td>
<td>1.17-4.24</td>
<td>2.16</td>
</tr>
</tbody>
</table>

Model 1: Unadjusted

Model 2: Adjusted for Demographics

Model 3: Adjusted for Demographics, Co-morbidities (Hypertension, Smoking, History of Ischemic Stroke, Diabetes), Body mass index, Low-density lipoprotein and High-density lipoprotein

Model 4: Adjusted for Demographics, Co-morbidities, and Statin use

Results

• Approximately 70% of recurrent ischemic strokes were lacunes.

• Results for lacunar stroke consistent with the effect on ischemic stroke (adj HR 2.27, 95% CI 0.90-5.75).

• No interactions with:
  • dual antiplatelet therapy
  • BP targets
  • Statin use


• Use of Inflammatory Biomarkers in Primary Prevention
  – Unlikely to be of value for general screening or for use in high risk or low risk populations
  – hsCRP associated with many other risk factors
  – HsCRP and LpPLA2 levels may be of incremental value in identification of patients at increased risk of stroke and other events, particularly for those at intermediate risk

• Use of Inflammatory Biomarkers in Secondary Prevention
  – CRP is an acute phase protein and is associated with severity of stroke
  – CRP and LpPLA2 may provide complementary information after stroke in general; CRP may be a better predictor of mortality while LpPLA2 may better predict risk of recurrent stroke and other vascular events
  – HsCRP may be a better prognostic marker in less severe stroke (lacunar stroke), or when measured at an interval of several weeks after stroke
  – Effect of hsCRP has a threshold rather than a continuous relationship.
  – HsCRP levels do not predict response to dual antiplatelet therapy or BP targets.

Inflammation: Potential trials in secondary prevention

1. Use of CRP to stratify patients as being at high risk after lacunar stroke/mild stroke
   a. Improve power when testing an intervention
   b. Limit risks to a high-risk population

2. Anti-inflammatory therapies:
   a. Test for interaction of a therapy with biomarkers
   b. Drugs
      i. Statins
      ii. Methotrexate
      iii. LpPLA2 inhibitor (Darapladib)
      iv. Others

STABILITY: Darapladib
Primary End Point of Death from Cardiovascular Causes, Myocardial Infarction, or Stroke

Primary and Secondary Efficacy End Points

JUPITER: Cumulative incidence of stroke according to study group

Rosuvastatin reduced risk of first stroke by 50% among those with hsCRP >2 mg/L.

Circulation Everett BM et al. Circulation 2010;121:143-150

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Outline

- Inflammatory markers and stroke risk
- Chronic infections and stroke risk
- Acute infection and stroke risk
- Anti-inflammatory treatments

**The response-to-injury hypothesis of atherosclerosis**

- Oxidized LDL, Homocysteine, Toxins, Mechanical forces, Infectious agents
- Endothelial injury/dysfunction
- Monocyte and T lymphocyte adhesion, diapedesis, subendothelial localization
- Lipid accumulation, Foam cell formation, Macrophage activation, Cytokine/GF release
- Smooth muscle proliferation/Fibrous plaque formation


**Infection and Stroke**

**C. pneumoniae** is capable of infecting endothelia, monocytes, and smooth muscle cells

- **C. pneumoniae** identified by:
  - EM in coronary atheroma
  - PCR/Immunocytochemistry in coronary, aortic, and carotid atheromas
  - Culture in coronary and carotid arteries

Grayston et al. Circulation 1995
Jackson et al. J Inf Dis 1997

**“Burden” of Infectious Disease?**

- **THE “STROKE” BUG**
  - **ATHEROSCLEROSIS**
  - **STROKE**

Elkind MSV. Infect Disord Drug Targets 2010;9(5).
Results (n=1625)

First stroke

Positive Serology                      Adjusted HR* (95 % CI)

*C. pneumoniae IgA 1.30 (0.75 – 2.25)
H. pylori IgG 1.13 (0.68 – 1.89)
CMV IgG 2.19 (0.84 – 5.70)
HSV 1 IgG 1.35 (0.59 – 3.07)
HSV 2 IgG 1.59 (0.91 – 2.76)

*Adjusted for age, sex, race-ethnicity, high school education, CAD, systolic BP, HDL, LDL, blood sugar, alcohol, smoking, waist circumference, physical activity.


Results (n=1625)

Serologies Unadjusted Parameter estimate

Parameter
Infectious burden index

C. Pneumoniae IgA 0.265 + 0.265
H. Pylori IgG -0.086 - 0
CMV IgG 0.685 + 0.685
HSV 1 IgG 0.220 - 0
HSV 2 IgG 0.177 + 0.177

Total score 1.127

Hypothetical participant

Infectious burden index: mean 1.00 ± 0.33, median 1.08


Results (n=1625)

Infectious burden and risk of first stroke

<table>
<thead>
<tr>
<th></th>
<th>HR (95 % CI) per SD IBI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Among full cohort (n=1625)</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.39 (1.04 – 1.87)</td>
</tr>
<tr>
<td>Adjusted for demographics*</td>
<td>1.42 (1.04 – 1.94)</td>
</tr>
<tr>
<td>Adjusted for demographics* and risk factors†</td>
<td>1.39 (1.02 – 1.90)</td>
</tr>
<tr>
<td>Adjusted for demographics*, risk factors*, and log hsCRP</td>
<td>1.39 (1.02 – 1.90)</td>
</tr>
<tr>
<td>Adjusted for demographics, risk factors*, and log leukocyte count</td>
<td>1.40 (1.03 – 1.91)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, race-ethnicity, education, history of CAD, blood sugar, SBP, waist circumference, HDL, LDL, smoking, alcohol consumption, physical activity.


Maximal Carotid Plaque Thickness (MCPT):

<table>
<thead>
<tr>
<th></th>
<th>Change MCPT per SD IBI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>0.054 mm</td>
<td>0.07</td>
</tr>
<tr>
<td>Adjusted for demographics*</td>
<td>0.079 mm</td>
<td>0.01</td>
</tr>
<tr>
<td>Adjusted for demographics and risk factors**</td>
<td>0.087 mm</td>
<td>0.006</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, race-ethnicity, education
**Adjusted for above and history of CAD, blood sugar, SBP, waist circumference, HDL, LDL, smoking, alcohol consumption, physical activity.

NOMAS: Nested case-control study (n=172 cases/344 controls)
Endpoint: all ischemic strokes
- Elevated Procalcitonin and MRproANP levels, but not copeptin, predicted ischemic stroke

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copeptin</td>
<td>0.82</td>
<td>0.43 - 1.59</td>
</tr>
<tr>
<td>MRproANP</td>
<td>1.34</td>
<td>0.70 - 2.35</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>1.73</td>
<td>0.86 - 3.43</td>
</tr>
<tr>
<td>Copeptin</td>
<td>1.15</td>
<td>0.62 - 2.14</td>
</tr>
<tr>
<td>MRproANP</td>
<td>1.37</td>
<td>0.75 - 2.32</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>1.76</td>
<td>0.89 - 3.45</td>
</tr>
<tr>
<td>Copeptin</td>
<td>1.24</td>
<td>0.53 - 2.71</td>
</tr>
<tr>
<td>MRproANP</td>
<td>3.45</td>
<td>1.58 - 7.33</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>1.98</td>
<td>1.02 - 3.83</td>
</tr>
</tbody>
</table>

* Adjusted for demographics (age, sex, race, education) & medical risk factors (diabetes mellitus, hypertension, coronary artery disease, physical activity, alcohol consumption, smoking, LDL, HDL, eGFR)

Katan M et al. ISC 2014.

Cardiovascular Health Study
Sponsored by the National Heart, Lung and Blood Institute with additional contribution from the National Institute of Neurological Disorders and Stroke

http://chs-nhlbi.org

Methods
- CHS Recruitment and Enrollment
  - Multi-center prospective study of vascular risk factors in an elderly population-based cohort
  - Random sample of men and women > 65 years recruited from Medicare eligibility lists in four U.S. communities:
    - Sacramento County, California
    - Washington County, Maryland
    - Forsyth County, North Carolina
    - Pittsburgh, Pennsylvania
  - The CHS enrolled 5888 participants 1989-93

Results

Baseline Characteristic Case-Crossover Analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>669 (11.4)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>74.0 ± 5.7</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>408 (61.0)</td>
<td></td>
</tr>
<tr>
<td>Self-reported race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>101 (15.1)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>566 (84.6)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Current Smoker</td>
<td>74 (11.1)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>132 (19.7)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>396 (59.5)</td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol in mg/dL</td>
<td>213.4 ± 45.2</td>
<td></td>
</tr>
</tbody>
</table>


Results

General infection ICD-9 code(s) Frequency (%) of infections during 90-day case period Frequency (%) of infections during BOTH 90-day control periods

<table>
<thead>
<tr>
<th>Infection Class</th>
<th>Code(s)</th>
<th>Frequency (%)</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>460-466, 480-487</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>599.0, 595, 596</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Skin and subcutaneous</td>
<td>680-686</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>790.7</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>730.0-730.2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Assorted</td>
<td>001-134</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>TOTAL</td>
<td>36</td>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>


Results

Association of recent hospitalization for infection with ischemic stroke: Case-crossover analysis

<table>
<thead>
<tr>
<th>Exposure to Hospitalization within:</th>
<th>Case intervals, n</th>
<th>Control intervals, n</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 days prior to stroke</td>
<td>631</td>
<td>1179</td>
<td>3.4</td>
<td>1.8-6.5</td>
</tr>
<tr>
<td>30 days prior to stroke</td>
<td>655</td>
<td>1193</td>
<td>7.3</td>
<td>1.9-40.9</td>
</tr>
<tr>
<td>14 days prior to stroke</td>
<td>660</td>
<td>1194</td>
<td>8.0</td>
<td>1.6-77.3</td>
</tr>
</tbody>
</table>


Results

Risk of ischemic stroke during the time interval after hospitalization for infection: Time-dependent survival analysis

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 days</td>
<td>Unadjusted: 4.4 (2.2-9.3) Adjusted for age, sex, race: 4.0 (2.0-8.2) Adjusted for above, DM, and smoking: 3.9 (1.9-8.0) Adjusted for above, common carotid IMT: 3.9 (1.9-7.9)</td>
</tr>
<tr>
<td>30 days</td>
<td>2.9 (1.6-5.3)</td>
</tr>
<tr>
<td>90 days</td>
<td>2.9 (2.0-4.2)</td>
</tr>
</tbody>
</table>


Exposure: Influenza-like Illness

HCUP/AHRQ State Inpatient Databases:
California 2007-2009
Acute Influenza-like Illness and Ischemic Stroke
Results
• Total stroke cases n=41,148
• Median (IQR) age of cases was 74 (62-83) years
• 52.4% were women
• 90-Day ILI Distribution, By Year
  – Year of stroke, 2009 n=439
  – Year prior to stroke, 2008 n=303
  – 2 years prior to stroke, 2007 n=81

Multivariate Adjusted Results

<table>
<thead>
<tr>
<th>Risk Window</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-DAY</td>
<td>6.5</td>
<td>2.2-19.7</td>
</tr>
<tr>
<td>30-DAY</td>
<td>3.7</td>
<td>1.8-8.3</td>
</tr>
<tr>
<td>90-DAY</td>
<td>3.3</td>
<td>2.0-5.8</td>
</tr>
</tbody>
</table>

Age Strata, 30-Day window

<table>
<thead>
<tr>
<th>Stratum</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;45</td>
<td>16.6</td>
<td>1.0-267.2</td>
</tr>
<tr>
<td>45 to &lt;=65</td>
<td>5.4</td>
<td>1.1-27.5</td>
</tr>
<tr>
<td>&gt;65</td>
<td>2.5</td>
<td>1.0-6.8</td>
</tr>
</tbody>
</table>

Age-Adjusted Incidence Ratios of a Stroke during Risk Periods after Exposure to Vaccination or Infection

Infection:
• Infectious burden may be associated with long-term stroke risk
• Acute infections are likely associated with near-term stroke risk (i.e., stroke trigger)
• Influenza vaccination can reduce risk of stroke/vascular disease
  • AHA/JACC Guidelines
• Recognition of this fact could have implications for management of patients presenting with infectious disorders, though this remains to be determined

Shifting paradigms in prevention

Vulnerable plaque
→
Vulnerable patient


Vulnerable time period

Infection: Potential trials in prevention

1. Flu vaccination to prevent stroke (primary/secondary)
2. Identification of patients at increased LONG-TERM stroke risk due to infectious burden or related markers for drug therapy
   a. Antibiotics
   b. Anti-inflammatories
3. Identification of patients at increased NEAR-TERM stroke risk due to acute or recent infection (URI, flu, UTI, etc) and treat with vascular protective agent (ASA, statins, etc)
Outline

- Inflammatory markers and stroke risk
- Infectious markers and stroke risk
- Acute infection and stroke risk
- Acute stroke: Anti-inflammatory treatments
  - Statins
  - Natalizumab

Cholesterol-Independent Effects of the Statins

- Upregulation of endothelial NOS
  Improves vascular reactivity
  Increased coronary and cerebral blood flow
- Anti-inflammatory
  Lowers CRP and LpPLA2
  Inhibits macrophage adhesion and diapedesis
- Reduction in free radicals
- Decreased platelet activation, thrombus formation
- Increased fibrinolysis
- Increased angiogenesis

Neuroprotection
Statins reduce infarct volume in a rat model of stroke

Treatment with simvastatin up 20 mg/kg at 3 hours after MCA occlusion


Meta-analysis of statin therapy: Forest plots of 90-day outcomes (good functional outcome and death) with statin treatment at stroke onset, in observational studies

Functional outcomes

Mortality

NeuSTART Phase 1 RESULTS

Table 3. Model-based probabilities of dose-limiting toxicity

<table>
<thead>
<tr>
<th>Statin</th>
<th>Tier</th>
<th>Prior</th>
<th>Final 90% posterior</th>
<th>90% posterior interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>0.02</td>
<td>0.01</td>
<td>0.00, 0.07</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>0.06</td>
<td>0.03</td>
<td>0.00, 0.15</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>0.10</td>
<td>0.06</td>
<td>0.01, 0.21</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>0.18</td>
<td>0.13</td>
<td>0.03, 0.31</td>
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<tr>
<td>5</td>
<td>8</td>
<td>0.30</td>
<td>0.24</td>
<td>0.08, 0.44</td>
</tr>
</tbody>
</table>


NeuSTART Phase 2

Objectives:

- **Primary Aim:** To determine whether lovastatin 640 mg daily for 3 days beginning within 24 hours after acute stroke can be administered safely (<10 percentage points higher risk of myotoxicity and/or hepatotoxicity).
- **Secondary Aim:** To assess efficacy of lovastatin administered at high doses.

Natalizumab: exploring its potential in acute ischemic stroke

- Natalizumab (BG00002) is a recombinant humanized monoclonal antibody
  - Blocks α4β1-integrin-mediated adhesion of leukocytes to vascular endothelial cells
  - Inhibits transmigration of leukocytes into inflamed parenchymal tissue
  - Well-characterized safety profile and established efficacy in relapsing multiple sclerosis and Crohn’s disease1
  - Low risk of developing progressive multifocal leukoencephalopathy (PML) from a single dose
- Antibodies targeting α4 reduce infarct volume and improve functional outcomes vs placebo in animal models2
- Models of inflammation in stroke indicate an approx 6-hour time window is relevant for natalizumab action3

Anti-CD49d treatment (natalizumab) inhibits leukocyte migration into the ischaemic brain

Liesz A et al. Brain 2011;134:704-720

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What is the ACTION Study?

• Double-blind, randomized, phase II study to assess the efficacy and safety of intravenous natalizumab in reducing infarct volume in acute ischemic stroke
• Randomizing 200 patients with acute ischemic stroke
• Approximately 50 sites in the US and Europe

Primary objective: To determine whether one 300 mg dose of intravenous (IV) natalizumab reduces change in infarct volume from Baseline to Day 5 on magnetic resonance imaging (MRI) in patients with acute ischemic stroke when given at ≤ 6 hours or at >6 to ≤ 9 hours from when they were last known normal (LKN).

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Thanks for your attention!