Stroke Update

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Disclosures

- Consultant: Abbott Vascular, Biogen, Lundbeck
- Scientific Advisory Board: Silk Road Medical
- Investigator: ACT 1, CREST 2, SAMMPRIS, SWIFT-PRIME, ESCAPE
Cerebrovascular Disease: the Problem

- 800,000 new strokes each year
- 5<sup>th</sup> leading cause of death
- 4.7 million stroke survivors in US
- Leading cause of disability in adults
- $40-50 billion per year overall cost
- Of those who survive, 90% have deficit
- Future prediction of >1 million strokes/year

T. Kitago. ISC 2016
Cerebrovascular Disease: Stroke Subtype

**Hemorrhagic Stroke (17%)**
- Intracerebral Hemorrhage (59%)
- Subarachnoid Hemorrhage (41%)

**Ischemic Stroke (83%)**
- Atherothrombotic Cerebrovascular Disease (20%)
- Cryptogenic (30%)
- Lacunar (25%)
- Small vessel disease
- Embolism (20%)

Stroke Treatment

- Risk factor management
- Antiplatelet agents
- Anticoagulants
- Carotid revascularization
- Acute stroke therapy
  - IV tPA
  - Endovascular therapy
Risk Factor Control

- Hypertension - $\leq 140/90, 130/80$ DM
- Dyslipidemia - LDL $< 70-80$
- Diabetes - HbA1c $< 7.0$
- Lifestyle modification
  - Exercise
  - Diet
  - Weight reduction
  - Smoking cessation
- Obstructive sleep apnea
- Eliminate heavy alcohol
Aspirin Efficacy by Dose: Meta-Analyses in Patients With Stroke or TIA*

* Endpoint: stroke, MI, or vascular death

<table>
<thead>
<tr>
<th>Dose (mg/day)</th>
<th>RRR (%) ± 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 – 100</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td></td>
</tr>
<tr>
<td>75 – 300</td>
<td></td>
</tr>
<tr>
<td>300</td>
<td></td>
</tr>
<tr>
<td>900 – 1500</td>
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<tr>
<td>900 – 1500</td>
<td></td>
</tr>
<tr>
<td>650 – 1500</td>
<td></td>
</tr>
</tbody>
</table>

Dose (mg/day):
- Low Dose: 50 – 100
- Medium Dose: 75 – 300
- High Dose: 900 – 1500

* Algra, van Gijn
* Johnson

* Endpoint: stroke, MI, or vascular death
CAPRIE Study
Efficacy of Clopidogrel in Primary Analysis
MI, Ischemic Stroke, or Vascular Death

CAPRIE Steering Committee. Lancet 1996
CHANCE Trial

- Randomized double blind trial of clopidogrel + asa v. asa alone within 24 hours of minor stroke or high risk TIA.
- 5170 pts in 114 centers in China
- 3.5% absolute reduction in stroke events over 90 days
- No increase in hemorrhages.

Wang et al. NEJM 2013
Atrial Fibrillation and Stroke: Summary of Randomized Studies

Afib Stroke Risk Stratification

- **CHADS2**
  - CHF
  - Hypertension
  - Age > 75
  - Diabetes
  - Prior CVA/TIA (2)
  - Maximal Score – 6
  - 0 ASA, 1 ASA/AC, > 2 AC

- **CHA2DS2 VASC**
  - CHF
  - Hypertension
  - Age < 65 (0)
  - Age 65-74 (1)
  - Age > 74 (2)
  - Diabetes
  - Prior CVA/TIA (2)
  - Vascular disease
  - Male (0)
  - Female (1)
  - Maximal Score - 9
  - 0 ASA, 1 ASA/AC, > 2 AC
WARFARIN VS. ASPIRIN FOR RECURRENT STROKE STUDY (WARSS)

- 2206 patients over 2 years
- Randomized, double blinded study
- Non-cardioembolic stroke, non-operable atherosclerotic disease within 30 days of event
- Warfarin INR 1.4-2.8 v. ASA 325 mg
- Primary endpoint – recurrent ischemic stroke or death
- Secondary endpoints – TIA, MI
- No difference in ischemic events or hemorrhage rate over 2 yr followup

# New Anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td>Direct thrombin inh</td>
<td>Factor Xa inhibitor</td>
<td>Factor Xa inhibitor</td>
<td>Factor Xa inhibitor</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>Twice daily</td>
<td>Once daily</td>
<td>Twice daily</td>
<td>Once daily</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>2-3 hrs</td>
<td>3 hrs</td>
<td>3 hrs</td>
<td>1-3 hrs</td>
</tr>
<tr>
<td><strong>Half life</strong></td>
<td>12-17 hrs</td>
<td>7-11 hrs</td>
<td>9-14 hrs</td>
<td>10-14 hrs</td>
</tr>
<tr>
<td><strong>Clearance</strong></td>
<td>Renal</td>
<td>Renal</td>
<td>GI/Renal</td>
<td>GI/Renal</td>
</tr>
</tbody>
</table>
New Anticoagulants

Advantages
- No monitoring
- Rapid onset of action
- Once or twice daily
- Lower stroke risk
- Reduced overall bleeding risk
- Reduced ICH
- Fewer interactions

Disadvantages
- No reversal agent
- Increased GI bleeds
- Compliance important
- Expense
- Renal adjustment
Cardiac Monitoring

EMBRACE

- RCT 572 pts with cryptogenic stroke and no Afib by 24 hr monitoring
- Randomized to 30 day cardiac monitoring or one additional 24 hr monitor
- Afib within 90 days in 16.1% v. 3.2% of patients

CRYSTAL AF

- RCT 441 pts with cryptogenic stroke and no Afib by 24 hr monitoring
- Randomized to insertable cardiac monitoring or conventional follow-up
- Afib within 36 mo in 30% v. 3% of patients

Gladstone et al. NEJM 2014
Sanna et al. NEJM 2014
What We Know About PFOs

- Present in ~ 10 - 12% of population
- Found in up to 26% on autopsy
- Greater frequency in patients with stroke
- Even greater frequency (45-55%) in young patients with cryptogenic stroke
- Causative or innocent bystander?
- Does endovascular closure prevent recurrent stroke?
### PFO Device RCTs

<table>
<thead>
<tr>
<th></th>
<th>CLOSURE</th>
<th>RESPECT</th>
<th>PC TRIAL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pts</strong></td>
<td>909</td>
<td>980</td>
<td>414</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Superiority</td>
<td>Endpoint</td>
<td>Superiority</td>
</tr>
<tr>
<td><strong>Inclusion</strong></td>
<td>Stroke and TIA</td>
<td>Stroke</td>
<td>Stroke, TIA*, Emb</td>
</tr>
<tr>
<td><strong>Endpoint</strong></td>
<td>Stroke, TIA, Dth</td>
<td>Stroke, Dth</td>
<td>Str, TIA, Dth, Emb</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>2 yrs</td>
<td>25 endpoints</td>
<td>4 yrs</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>5 yrs</td>
<td>8 yrs</td>
<td>10 yrs</td>
</tr>
<tr>
<td><strong>Device event rate</strong></td>
<td>3.1% (1.5% yr)</td>
<td>2.2% (0.44%/yr)</td>
<td>3.4% (0.85%/yr)</td>
</tr>
<tr>
<td><strong>Medical event rate</strong></td>
<td>3.4% (1.7% yr)</td>
<td>6.5% (1.3%/yr)</td>
<td>5.2% (1.3%/yr)</td>
</tr>
</tbody>
</table>

* Documented MRI lesion
RESPECT Trial: 10 yr results

- PFO closure effective over longer term
- Prevents cryptogenic stroke, not other types

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>Risk Reduction</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td>0.55 (0.30-0.99)</td>
<td>45%</td>
<td>0.046</td>
</tr>
<tr>
<td>Stroke of unknown mechanism</td>
<td>0.38 (0.18-0.79)</td>
<td>62%</td>
<td>0.007</td>
</tr>
<tr>
<td>Age &lt; 60 yrs</td>
<td>0.42 (0.21-0.83)</td>
<td>58%</td>
<td>0.010</td>
</tr>
</tbody>
</table>

Thaler et al. TCT 2016
### CEA: Pooled Data Symptomatic Randomized Trials

<table>
<thead>
<tr>
<th>% Stenosis</th>
<th>n</th>
<th>ARR (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30</td>
<td>1746</td>
<td>-2.2</td>
<td>.05</td>
</tr>
<tr>
<td>30 – 49</td>
<td>1429</td>
<td>3.2</td>
<td>.6</td>
</tr>
<tr>
<td>50 – 69</td>
<td>1549</td>
<td>4.6</td>
<td>.04</td>
</tr>
<tr>
<td>&gt; 70 Without near-occlusion</td>
<td>1095</td>
<td>16.0</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

## Asymptomatic Stenosis RCTs: CEA v. Medical Therapy

<table>
<thead>
<tr>
<th></th>
<th>Years</th>
<th>Pts</th>
<th>F/U</th>
<th>Str-Dth/Yr Med</th>
<th>Str-Dth/Yr Surg</th>
<th>ARR / Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>VACS</td>
<td>1983-1987</td>
<td>444</td>
<td>4 yrs</td>
<td>2.4%*</td>
<td>1.2%*</td>
<td>1.2%*</td>
</tr>
<tr>
<td>ACAS</td>
<td>1987-1993</td>
<td>1659</td>
<td>5 yrs</td>
<td>2.2%</td>
<td>1%</td>
<td>1.2%</td>
</tr>
<tr>
<td>ACST</td>
<td>1993-2003</td>
<td>3120</td>
<td>5 yrs</td>
<td>2.4%</td>
<td>1.3</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

* ipsilateral nonfatal and fatal stroke

Carotid Stenting: an Emerging Option
## CREST Results

<table>
<thead>
<tr>
<th></th>
<th>CAS</th>
<th>CEA</th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Endpoint ≤ 4 yrs</strong>*</td>
<td>7.2%</td>
<td>6.8%</td>
<td>1.11</td>
<td>0.81-1.51</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>Periprocedural Stroke</strong></td>
<td>4.1%</td>
<td>2.3%</td>
<td>1.79</td>
<td>1.14-2.82</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Periprocedural MI</strong></td>
<td>1.1%</td>
<td>2.3%</td>
<td>0.50</td>
<td>0.26-0.94</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Major Stroke</strong></td>
<td>0.9%</td>
<td>0.6%</td>
<td>1.35</td>
<td>0.54-3.36</td>
<td>0.52</td>
</tr>
<tr>
<td><strong>Ipsilateral Stroke up to 4 yrs</strong></td>
<td>2.0%</td>
<td>2.4%</td>
<td>0.94</td>
<td>0.50-1.76</td>
<td>0.85</td>
</tr>
</tbody>
</table>

*Any periprocedural stroke, MI, death plus ipsilateral stroke thereafter*
### Oxford Vascular Study

**Stroke Risk with ≥ 50% Carotid Stenosis**

- Population based study of 1153 pts with stroke or TIA recruited between 2002 – 2009
- All pts treated with intensive medical therapy – AP, statins, BP reduction, lifestyle changes
- 101 (8.8%) with ≥ 50% asymptomatic stenosis
- Mean followup 3 years

<table>
<thead>
<tr>
<th>Event</th>
<th>Number</th>
<th>% / yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral minor stroke</td>
<td>1</td>
<td>0.34%</td>
</tr>
<tr>
<td>Ipsilateral major stroke</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>TIA</td>
<td>5</td>
<td>1.78%</td>
</tr>
</tbody>
</table>

Marquardt et al. Stroke 2010
CREST-2 Parallel Study Design

(n = 1,240 in each trial)

ือน = Screened

R = Randomized

Endpoint = all stroke & death in first 30 days and ipsilateral stroke thereafter up to 4 years.
## Intensive Medical Therapy

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Goal</th>
<th>Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Risk Factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL</td>
<td>&lt; 70 mg/dL</td>
<td>Local lab</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>&lt; 140 mm Hg</td>
<td>Measured each visit</td>
</tr>
<tr>
<td><strong>Secondary Risk Factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-HDL</td>
<td>&lt; 100 mg/dL</td>
<td>Local lab</td>
</tr>
<tr>
<td>HgA1c</td>
<td>&lt; 7.0%</td>
<td>Local lab</td>
</tr>
<tr>
<td>Smoking</td>
<td>Cessation</td>
<td>Self</td>
</tr>
<tr>
<td>Weight management</td>
<td>BMI &lt;25 kg/mm2 or 10%</td>
<td>Weight at each visit</td>
</tr>
<tr>
<td>Exercise</td>
<td>&gt; 30 min 3 X per week</td>
<td>Self</td>
</tr>
</tbody>
</table>
Time Is Brain: Effects of IV tPA vs Time

mRS 0-1 at day 90

Adjusted odds ratio with 95 % confidence interval by stroke onset to treatment time (OTT)

< 3 h  3-4.5 h

Limitations of IV tPA

- 3-4.5 hour time window
- Less effective for large artery occlusion – less than 50% recanalization
- Early reocclusion in 20 – 30%
- Adjunctive therapy might improve results
MR CLEAN Trial: Effect of Intervention on Primary Outcome

Common adjusted odds ratio: 1.67 (95% CI: 1.21 to 2.30)

Berkhemer et al. NEJM 2015
# Next Generation Device Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Pts</th>
<th>Control</th>
<th>Window</th>
<th>Selection</th>
<th>Endpoint</th>
<th>Diff</th>
<th>NNT</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR CLEAN</td>
<td>500</td>
<td>Best Med</td>
<td>&lt; 6 hrs</td>
<td>NIHSS &gt; 2; Grey area principle</td>
<td>mRs 0-2</td>
<td>14%</td>
<td>7</td>
<td>1.7**</td>
</tr>
<tr>
<td>ESCAPE</td>
<td>314</td>
<td>Best Med</td>
<td>&lt; 12 hrs</td>
<td>NIHSS &gt; 5; ASPECT &gt; 5; P2P &lt; 60 min; P2R &lt; 90 min</td>
<td>mRS 0-2 or NIHSS 0-2</td>
<td>24%</td>
<td>4</td>
<td>2.6**</td>
</tr>
<tr>
<td>EXTEND-IA</td>
<td>70</td>
<td>IV tPA</td>
<td>&lt; 6 hrs</td>
<td>Core &lt; 70 cc; Penumbra &gt; 10 cc</td>
<td>Reperfusion 24 hrs</td>
<td>31%</td>
<td>3</td>
<td>3.8</td>
</tr>
<tr>
<td>SWIFT-PRIME</td>
<td>196</td>
<td>IV tPA</td>
<td>&lt; 6 hrs</td>
<td>ASPECT &gt; 6; NIHSS &gt; 7</td>
<td>mRS 0-2*</td>
<td>25%</td>
<td>4</td>
<td>2.8</td>
</tr>
<tr>
<td>REVASCAT</td>
<td>195</td>
<td>IV tPA</td>
<td>&lt; 8 hrs</td>
<td>NIHSS &gt; 5; ASPECT &gt; 6</td>
<td>mRS 0-2</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

* SWIFT-PRIME primary Rankin shift, mrs 0-2 secondary

** Rankin shift

NR – Not reported
<table>
<thead>
<tr>
<th>Treatment</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI to prevent MI</td>
<td>30</td>
</tr>
<tr>
<td>IV tPA – additional good outcome</td>
<td>8</td>
</tr>
<tr>
<td>EVT – additional good outcome</td>
<td>3-4</td>
</tr>
</tbody>
</table>
Reducing Time to Treatment

- EMS education
- Hospital prenotification
- Preorder testing
- Immediate CT read
- Premix tPA
- Exam on CT table
- Hx during transport

- Prehospital
  - Detection
  - Dispatch
  - Delivery

- Post arrival
  - Door
  - Data
  - Decision
  - Drug

Meretoja et al. Neurology 2012
Mobile Stroke Unit

- Ambulance
- Portable CT
- POC lab
- Telemedicine
- Teleradiology

Rajan et al. JAMA Neurol 2014
Summary

- Stroke is a leading cause of death and disability in US and worldwide
- Many recent advances in stroke diagnosis and treatment
- IV tPA effective 3-4.5 hrs after stroke
- Mechanical thrombectomy is highly effective in appropriate patients and should be standard of care
- Transport and triage of acute stroke must be reorganized to deliver the right patient to the right hospital for the right therapy at the earliest time.
THANK YOU!