Updates in Stroke Diagnosis, Management, and Prevention

Robin Dharia, MD
Division of Cerebrovascular Disease
Director of Quality Improvement & Patient Safety, Department of Neurology
Director, Acute Stroke Unit
Clinical Assistant Professor, Sidney Kimmel Medical College
Disclosures

• None
Topics for Discussion

- Background & Stroke Basics
- Diagnosis
- Acute ischemic stroke update
- TIA/Minor stroke
- Secondary stroke prevention
- Intracranial stenosis
- Dissection
- Cryptogenic stroke
- Carotid stenosis
- Intracerebral hemorrhage
- Outpatient stroke care
Topics for Discussion

- Background & Stroke Basics
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Vascular Neurology

Conditions Treated:
- Primary Prevention of Stroke
- Ischemic Stroke
- Intracerebral Hemorrhage
- Transient Ischemic Attack
- Carotid Disease
- Dissection
- Vascular Malformations
- Intracranial Stenosis
- Cerebral Venous Sinus Thrombosis
- Moyamoya Disease
- Cerebral Small Vessel Disease
- CNS Vasculitis
- Pre-operative Stroke Risk Evaluation
- Vertebralbasilar Insufficiency
- Stroke in Young Patients
- Cryptogenic Stroke
- Stroke and PFO
- Stroke and Pregnancy
- Genetic/Inherited Stroke
- Amaurosis Fugax
- Vascular Dementia
- Central Retinal Artery Occlusion
- Post-stroke Spasticity
- Cerebral Aneurysm
- Subarachnoid Hemorrhage
- Post-stroke Migraine, Seizures, Depression
- Spinal Cord Infarct
- Reversible Cerebral Vasoconstriction Syndrome
Time is Brain

- Every minute during a stroke:
  - 1.9 million neurons die
  - 14 billion synapses are lost

<table>
<thead>
<tr>
<th></th>
<th>Neurons Lost</th>
<th>Synapses Lost</th>
<th>Myelinated Fibers Lost</th>
<th>Accelerated Aging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per Stroke</td>
<td>1.2 billion</td>
<td>8.3 trillion</td>
<td>7140 km/4470 miles</td>
<td>36 y</td>
</tr>
<tr>
<td>Per Hour</td>
<td>120 million</td>
<td>830 billion</td>
<td>714 km/447 miles</td>
<td>3.6 y</td>
</tr>
<tr>
<td>Per Minute</td>
<td>1.9 million</td>
<td>14 billion</td>
<td>12 km/7.5 miles</td>
<td>3.1 wk</td>
</tr>
<tr>
<td>Per Second</td>
<td>32 000</td>
<td>230 million</td>
<td>200 meters/218 yards</td>
<td>8.7 h</td>
</tr>
</tbody>
</table>

Who Knew

• ~800,000 strokes a year in US
  • Nearly 1 of 4—are in people who have had a previous stroke
• In 2010, stroke care costs $73 billion in direct and indirect costs
  • Space shuttle program 1972-2011: $196 billion
• Affects 3x as many women as breast cancer
• For those 65 and older, ~50% have cognitive deficits and reduced mobility 6 months after a stroke
Stroke Risk

- By 2030, an additional 3.4 million adults (20.5% increase in prevalence from 2012)
  - highest increase projected to be in white Hispanic males
- Extracranial disease: whites > African Americans
- Intracranial disease: African Americans, Chinese > whites
- Asians - higher rates of ICH
- Approximately 10% of all strokes occur in ages 18 to 50, increasing incidence
Mortality

• 5th leading cause of death
• Stroke kills about 140,000 Americans each year—that’s 1 out of every 20 deaths
  • Every 4 minutes, someone dies from a stroke
• ~50% of stroke deaths occur outside of the hospital
• 8-12% of ischemic strokes die within 30 days (massive MCA up to 80%)
• 37-38% of hemorrhage patients die within 30 days
• 20% higher mortality in rural areas
Recurrence

- 1/3 of recurrent strokes (within 2 years) occur within the first month
- Mortality for recurrent stroke exceeds initial stroke
- Long-term cumulative recurrence rate is 14.1% in Stroke Data Bank and 25% over five years in the Northern Manhattan Stroke Study

### TABLE 16-3 Recurrence Risk by Ischemic Stroke Subtype in the Northern Manhattan Stroke Study

<table>
<thead>
<tr>
<th>Stroke Subtype</th>
<th>30-Day</th>
<th>1-Year</th>
<th>5-Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>All stroke</td>
<td>2%</td>
<td>8%</td>
<td>16%</td>
</tr>
<tr>
<td>Extracranial atherosclerotic</td>
<td>9%</td>
<td>11%</td>
<td>23%</td>
</tr>
<tr>
<td>Intracranial atherosclerotic</td>
<td>8%</td>
<td>12%</td>
<td>16%</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>4%</td>
<td>7%</td>
<td>21%</td>
</tr>
<tr>
<td>Lacunar</td>
<td>1.4%</td>
<td>10%</td>
<td>14%</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>0.4%</td>
<td>6%</td>
<td>15%</td>
</tr>
</tbody>
</table>
Stroke at Jefferson

• Ischemic strokes >900
• Hemorrhages >350
• TIAs > 400
• Thrombectomy >200
• 25+ network hospitals
• ~80 stroke alerts/month
• Mobile stroke unit, curb to tPA 20 min
15-20% of cardiac output is received by the brain.
Stroke Types

Ischemic Strokes
87% of all strokes:
• 20% large vessel
• 30% lacunar
• 30% cryptogenic
• 20% cardioembolic

Hemorrhagic Strokes
13% of strokes
• ICH: 70%
• SAH: 30%
Transient Ischemic Attack

• 1/3 of TIA patients go on to have a stroke within a year

• No difference in response to a TIA or a stroke
  • there is no way to predict which clots will dissolve on their own

• We need to understand why it happened and prevent a stroke from occurring
• 80% of strokes can be prevented
• High blood pressure is the leading risk factor for stroke
• About 77% of people who have a first stroke have average BP > 140/90 mm Hg

<table>
<thead>
<tr>
<th>Controllable Risk Factors</th>
<th>Non-Controllable Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Blood Pressure</td>
<td>Age</td>
</tr>
<tr>
<td>High Cholesterol</td>
<td>Gender</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Race</td>
</tr>
<tr>
<td>Tobacco Use</td>
<td>Family History</td>
</tr>
<tr>
<td>Alcohol Use</td>
<td>Previous Stroke or TIA</td>
</tr>
<tr>
<td>Physical Inactivity</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
</tr>
<tr>
<td>Heart Disease</td>
<td></td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td></td>
</tr>
</tbody>
</table>
The way neurologists think about stroke:

TOAST criteria

- Large artery atherosclerosis
- Cardioembolism
- Small vessel occlusion
- Stroke of other etiology
- Undetermined etiology

Classification

- At least one cardiac source of embolism can be detected in 50-70% of stroke patients by echo.
- $\frac{1}{4}$ of lacunar stroke patients also have ipsilateral large vessel disease.
- At least $\frac{1}{2}$ of stroke patients exhibit more than one etiology, 20% harbor multiple etiologies.
Topics for Discussion

- Background & Stroke Basics
- Diagnosis & Stroke syndromes
- Acute ischemic stroke update
- TIA/Minor stroke
- Secondary stroke prevention

- Intracranial stenosis
- Dissection
- Cryptogenic stroke
- Carotid stenosis
- Intracerebral hemorrhage
- Outpatient stroke care
Transcranial Doppler (TCD)

- Circle of Willis
- Direction, depth, velocity of blood flow
- Useful for detecting vasospasm in SAH, stenosis, sickle cell, collateral flow, occlusion, vascular malformations, microemboli, bubble study for shunting
- Noninvasive, low risk diagnostic test, no preparation required
Topics for Discussion

- Background & Stroke Basics
- Diagnosis
- Acute Ischemic Stroke Update
- TIA/Minor stroke
- Secondary stroke prevention
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Save the penumbra!

Ischaemic core (brain tissue destined to die)

Penumbra (salvageable brain area)
History of Acute Stroke Treatment

- Streptokinase - 1960s
- CT scan - 1970s
- Case series on intravenous thrombolysis - 1980s
- Intravenous tPA, NINDs trial - 1995
- Intra-arterial tPA - 1998
- Merci - 2004
- Penumbra - 2007
- Stent Retrievers - 2012
- Landmark thrombectomy trials published - 2015, 2017
AHA/ASA Guideline

Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

Endorsed by the Society for Academic Emergency Medicine and The Neurocritical Care Society

Reviewed for evidence-based integrity and endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons.
IV-tPA

- NINDS Trial 1995
- Treat up to 4.5 hours from onset
- In 2018, the contraindications and warnings for use of tPA were liberalized

Odds of a favorable 3-month outcome increased as onset to treatment decreased (p=0.005)
- 2.8 for 0-90 min
- 1.6 for 91-180 min
- 1.4 for 181-270 min
- 1.2 (for 271-360 min)
Intravenous tissue plasminogen activator

• Studies have found that <30% of patients present in time window for treatment
• About ¼ of eligible patients presenting within 2 hours of stroke onset fail to receive IV-tPA
NINDS TPA Stroke Trial

Excellent outcome at 3 months on all scales

Global outcome statistic: OR=1.7, 50% v. 38%= 12% benefit
Extending the tPA window to 9 hours

<table>
<thead>
<tr>
<th>A All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study</strong></td>
</tr>
<tr>
<td><strong>NIHSS</strong></td>
</tr>
<tr>
<td><strong>Region</strong></td>
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<tr>
<td><strong>Overall</strong></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Placebo (n=152)</th>
<th>Alteplase (n=152)</th>
<th>Odds ratio (95% CI)*</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>39/151 (26%)</td>
<td>55/152 (36%)</td>
<td>2.06 (1.17–3.62)</td>
<td>0.012</td>
</tr>
<tr>
<td>60/151 (40%)</td>
<td>77/152 (51%)</td>
<td>2.22 (1.25–3.94)</td>
<td>0.006</td>
</tr>
<tr>
<td>26/152 (17%)</td>
<td>44/148 (30%)</td>
<td>2.26 (1.26–4.03)</td>
<td>0.006</td>
</tr>
<tr>
<td>16/152 (11%)</td>
<td>20/152 (13%)</td>
<td>1.28 (0.60–2.73)</td>
<td>0.52</td>
</tr>
<tr>
<td>1/152 (1%)</td>
<td>7/152 (5%)</td>
<td>7.29 (0.88–60.18)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Data are n/N (%). mRS=modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. NA=not applicable. One patient in the placebo group did not have available mRS data at 3 months and was excluded from the analysis of the primary outcome and selected secondary outcomes. *Adjusted for baseline age and NIHSS. †Reduction of ≥1 point in mRS score (with mRS categories 5 and 6 merged), analysed using ordinal logistic regression. ‡Reduction of ≥8 points on NIHSS or reaching NIHSS score 0–1 at 72 h. §Within 36 h of treatment.

Table 4: Study outcomes in patients with automated perfusion mismatch (n=304)

Other thrombolytics

- **Tenecteplase**
  - May have better recanalization rates with lower bleed risk
  - Just as effective
  - Cheaper
  - Single bolus rather than infusion
Landmark Year in Stroke: 2015

- MR CLEAN
- REVASCAT
- ESCAPE
- SWIFT-PRIME
- EXTEND-IA

Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials


*Lancet 2016; 387: 1723-31*

Published Online
February 18, 2016
http://dx.doi.org/10.1016/
S0140-6736(16)00163-X
Endovascular thrombectomy within 12 hours of onset VS standard care

- **Primary outcome** - reduced disability mRs at 90 days
Figure 1: Scores on the modified Rankin Scale at 90 days
Distribution of scores at 90 days in the intervention and control groups in the overall trial population (A) and for patients treated with, or ineligible for, intravenous alteplase (B). Distributions for other subgroups shown in appendix pp 5–11.
What we learned

• The sooner the better

• Endovascular thrombectomy + best medical therapy more than doubles the odds of functional independence
How old is too old

- Consistent improvement in functional outcomes in all ages >80
- No reason to withhold thrombectomy solely on the basis of age
- Age still remains a strong independent predictor of final outcome
2017-2018

• Let’s expand the time window...the tissue window
Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct


DAWN (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo)
What have the results of DAWN revealed? TIME!

Occlusion of the intracranial ICA or proximal MCA
Thrombectomy 6-24 hours after last seen normal

→ Outcomes for functional independence at 90 days were better with thrombectomy + standard medical care
IV-tPA and Thrombectomy

- Treat eligible patients with IV alteplase even if endovascular therapy is being considered
- Do not delay administration for advanced imaging
The Future

• Large vessel occlusion and low NIHSS (minor symptoms) - to treat or not treat?
60 year old male
Topics for Discussion

- Background & Stroke Basics
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- Intracranial stenosis
- Dissection
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What are our options?

- Aspirin
- Clopidogrel
- Dipyridamole/Aspirin
- Cilostazol
- Ticagrelor
- DOACs
- LMWH
- Warfarin
Antiplatelets-Which one?

2. Aspirin (50–325 mg/d) monotherapy (Class I; Level of Evidence A) or the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily (Class I; Level of Evidence B) is indicated as initial therapy after TIA or ischemic stroke for prevention of future stroke. (Revised recommendation)

3. Clopidogrel (75 mg) monotherapy is a reasonable option for secondary prevention of stroke in place of aspirin or combination aspirin/dipyridamole (Class IIa; Level of Evidence B). This recommendation also applies to patients who are allergic to aspirin.

- Aspirin
- Clopidogrel
- Dipyridamole/asprin
- Cilostazol
- Ticagrelor
Stroke on Aspirin

• For patients who have an ischemic stroke or TIA while taking aspirin, there is no evidence that increasing the dose of aspirin provides additional benefit.

• No single agent or combination has been adequately studied in patients who have had a cerebrovascular event while receiving aspirin.
Dual antiplatelet therapy- long term?

• The combination of aspirin and clopidogrel, when initiated days to years after a minor stroke or TIA and continued for 2 to 3 years, increases the risk of hemorrhage relative to either agent alone and is not recommended for routine long-term secondary prevention after ischemic stroke or TIA.
Ticagrelor is not superior to aspirin in reducing the rate of stroke, MI, or death at 90 days.
16% RRR in recurrent stroke
RRR was 33% in carotid stenosis
A Comparison of Two LDL Cholesterol Targets after Ischemic Stroke

After ischemic stroke with evidence of atherosclerosis, target LDL <70 reduced the risk of subsequent CV events when compared to LDL 90-110

Table 2. Hazard Ratios for Adjudicated Clinical End Points.

<table>
<thead>
<tr>
<th>End Points</th>
<th>Lower-Target Group (N=1430)</th>
<th>Higher-Target Group (N=1430)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major cardiovascular event — no. (%)</td>
<td>121 (8.5)</td>
<td>156 (10.9)</td>
<td>0.78 (0.61–0.98)*</td>
<td>0.04</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>17 (1.2)</td>
<td>24 (1.7)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Fatal cerebral infarction or stroke of undeter-</td>
<td>3 (0.2)</td>
<td>6 (0.4)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>mined origin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal myocardial infarction</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Other cardiovascular death</td>
<td>7 (0.5)</td>
<td>6 (0.4)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Sudden death of undetermined origin</td>
<td>6 (0.4)</td>
<td>11 (0.8)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Nonfatal cerebral infarction or stroke of undet-</td>
<td>81 (5.7)</td>
<td>100 (7.0)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>mined origin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal acute coronary syndrome</td>
<td>15 (1.0)</td>
<td>23 (1.6)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Urgent coronary revascularization</td>
<td>5 (0.3)</td>
<td>6 (0.4)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Urgent carotid revascularization</td>
<td>3 (0.2)</td>
<td>3 (0.2)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>
DOACs

Besides afib, dvt, pe...

Cerebral venous sinus thrombosis, dissection, embolic appearing strokes, etc
Restarting anticoagulation

- When?
Topics for Discussion

- Background & Stroke Basics
- Diagnosis
- Acute ischemic stroke update
- Secondary stroke prevention
- TIA/Minor stroke

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- Dissection
- Cryptogenic stroke
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- Outpatient stroke care
TIA and Recurrence

- ~15-25% of all strokes are heralded by a TIA
- Meta-analyses- short-term risk of stroke after TIA to be ≈3% to 10% at 2 days and 9% to 17% at 90 days
- 10-year stroke risk ~19%
- Combined 10-year stroke, MI, or vascular death risk of 43% (4% per year)
- Minor neurological deficits (NIHSS 0-5) ≈ 50% of all strokes
  - Up to 30% may have unfavorable outcomes at 3 months
### Risk Factor

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\geq 60;\text{years}$</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Blood pressure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP $\geq 140;\text{mm;Hg}$ OR Diastolic BP $\geq 90;\text{mm;Hg}$</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical features of TIA</strong> (choose one)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral weakness with or without speech impairment OR Speech Impairment without unilateral weakness</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIA duration $\geq 60;\text{minutes}$</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>TIA duration 10-59 minutes</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

**Total ABCD$^2$ score** 0-7

### Using the ABCD$^2$ Score

Higher ABCD$^2$ scores are associated with greater risk of stroke during the 2, 7, 30, and 90 days after a TIA (Figure). The authors of the ABCD$^2$ score made the following recommendations for hospital observation:

<table>
<thead>
<tr>
<th>ABCD$^2$ Score</th>
<th>2-day Stroke Risk</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>1.0%</td>
<td>Hospital observation may be unnecessary without another indication (e.g., new atrial fibrillation)</td>
</tr>
<tr>
<td>4-5</td>
<td>4.1%</td>
<td>Hospital observation justified in most situations</td>
</tr>
<tr>
<td>6-7</td>
<td>8.1%</td>
<td>Hospital observation worthwhile</td>
</tr>
</tbody>
</table>

Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA

Question: is dual antiplatelet therapy superior to ASA monotherapy in prevention of recurrent stroke in patient with acute TIA or minor stroke?

Inclusion:
- Minor ischemic stroke (NIHSS score ≤3)
- High-risk TIA (ABCD² score ≥4)
- Randomized ≤12 hours of symptom onset
POINT

• 4,881 patients with acute ischemic stroke or high-risk TIA
• **Primary outcome:** Composite of ischemic stroke, MI, or ischemic vascular death
• **Randomization** to one of two groups:
  • **Aspirin group** received aspirin 50-325 mg/d (recommended 150-200 mg/d for 5 days followed by 75-100 mg/d) plus matching placebo
  • **Aspirin/clopidogrel group** received same aspirin dose as above, with **clopidogrel 600-mg loading dose** followed by 75 mg/d through **day 90**
A Primary Efficacy Outcome

<table>
<thead>
<tr>
<th>Groups</th>
<th>No. of Patients</th>
<th>No. with Event</th>
<th>Hazard ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>2449</td>
<td>160</td>
<td>0.75 (95% CI, 0.59–0.95)</td>
<td>0.02</td>
</tr>
<tr>
<td>Clopidogrel plus Aspirin</td>
<td>2432</td>
<td>121</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Days since Randomization

Patients with Event (%)
Primary Safety Outcome: Major Hemorrhage

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Patients</th>
<th>No. with Event</th>
<th>Hazard ratio, 95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>2449</td>
<td>10</td>
<td>2.32 (1.10–4.87)</td>
<td>0.02</td>
</tr>
<tr>
<td>Clopidogrel plus Aspirin</td>
<td>2432</td>
<td>23</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5. In patients presenting with minor stroke, treatment for 21 days with dual antiplatelet therapy (aspirin and clopidogrel) begun within 24 hours can be beneficial for early secondary stroke prevention for a period of up to 90 days from symptom onset.

The CHANCE trial (Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events) was a randomized, double-blind, placebo-controlled trial conducted in China to study the efficacy of short-term dual antiplatelet therapy begun within 24 hours, clopidogrel plus aspirin for 21 days followed by clopidogrel alone to 90 days, in patients with minor stroke (NIHSS score ≤3) or high-risk TIA (ABCD² [Age, Blood Pressure, Clinical Features, Duration, Diabetes] score ≥4). The primary outcome of recurrent stroke at 90 days (ischemic or hemorrhagic) favored dual antiplatelet therapy over aspirin alone (hazard ratio [HR], 0.68; 95% CI, 0.57–0.81; P<0.001). A subsequent report of 1-year outcomes found a durable treatment effect, but the HR for secondary stroke prevention was only significantly beneficial in the first 90 days. The generalizability of this intervention in non-Asian populations remains to be established, and a large phase III multicenter trial in the United States, Canada, Europe, and Australia is ongoing.

See Table XLV in online Data Supplement 1.
Ticagrelor and Aspirin or Aspirin Alone in Acute Ischemic Stroke or TIA

Is ticagrelor plus ASA superior to ASA alone in preventing recurrent disabling stroke at 30 days?
Combo reduced risk of stroke/death compared to aspirin alone (5.1% v. 6.3%)
Combo had increased risk of bleeding compared to aspirin alone (0.5% v. 0.1%)

**CHANCE 2: ticagrelor + aspirin VS clopidogrel + aspirin**
Topics for Discussion

• Background & Stroke Basics
• Diagnosis
• Acute ischemic stroke update
• TIA/Minor stroke
• Secondary stroke prevention
• Intracranial stenosis
• Dissection
• Cryptogenic stroke
• Carotid stenosis
• Intracerebral hemorrhage
• Outpatient stroke care
Intracranial atherosclerotic disease

- At least 8-10% of ischemic strokes
- Risk of recurrent stroke is high in patients with recent stroke or TIA and severe stenosis (70-99%)
Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis

Marc I. Chimowitz, M.B., Ch.B., Michael J. Lynn, M.S., Colin P. Derdeyn, M.D., Tanya N. Turan, M.D., David Fiorella, M.D., Ph.D., Bethany F. Lane, R.N., L. Scott Janis, Ph.D., Helmi L. Lutsep, M.D., Stanley L. Barnwell, M.D., Ph.D., Michael F. Waters, M.D., Ph.D., Brian L. Hoh, M.D., J. Maurice Hourihane, M.D., Elad I. Levy, M.D., Andrei V. Alexandrov, M.D., Mark R. Harrigan, M.D., David Chiu, M.D., Richard P. Klucznik, M.D., Joni M. Clark, M.D., Cameron G. McDougall, M.D., Mark D. Johnson, M.D., G. Lee Pride, Jr., M.D., Michel T. Torbey, M.D., M.P.H., Osama O. Zaidat, M.D., Zoran Rumboldt, M.D., and Harry J. Cloft, M.D., Ph.D., for the SAMMPRIS Trial Investigators*

2011
Maximal medical management

- Aspirin 325 mg + clopidogrel 75 mg for 90 days
- SBP <130
- LDL <70
- Management of other risk factors- DM2, tobacco abuse, obesity, lack of exercise, diet, OSA
Take home: for patients with recently symptomatic severe intracranial stenosis, aggressive medical management is superior to stenting

New stents/techniques are changing this practice
Anticoagulation in ICAD

• My take- Consider anticoagulation (DOAC/hep/VKA) for acute occlusions to prevent clot propagation and embolism. In 6-8 weeks, the thrombi become organized and adherent and collateral circulation develops. Switch to antiplatelet therapy around 3 months.

• Consider for severe stenosis until lumen improves and increases in size
Ticagrelor and large vessel disease
Topics for Discussion

- Background & Stroke Basics
- Diagnosis
- Acute ischemic stroke update
- TIA/Minor stroke
- Secondary stroke prevention
- Intracranial stenosis
- Dissection
- Cryptogenic stroke
- Carotid stenosis
- Intracerebral hemorrhage
- Outpatient stroke care
Antiplatelet treatment compared with anticoagulation treatment for cervical artery dissection (CADISS): a randomised trial

The CADISS trial investigators* 2015

In patients with extracranial carotid or vertebral artery dissection, does anticoagulation compared to antiplatelet agents reduce the risk of subsequent stroke or death?
Dissection Management

- My criteria for anticoagulation:
  - Presence of stroke
    - Provided risk of hemorrhagic conversion is not high
  - High grade stenosis due to dissection
  - Thrombus
  - Extra not intracranial dissection

- Repeating imaging 3-6 months and then adjust treatment
Topics for Discussion

- Background & Stroke Basics
- Diagnosis
- Acute ischemic stroke update
- TIA/Minor stroke
- Secondary stroke prevention

- Intracranial stenosis
- Dissection
- Cryptogenic stroke
- Carotid stenosis
- Intracerebral hemorrhage
- Outpatient stroke care
Embolic Stroke of Undetermined Source

- Implantable cardiac monitor
- Hypercoagulable work-up
- TTE w/bubble study
- TCDs w/bubble study or TEE
Rivaroxaban was not superior to aspirin with regard to the prevention of recurrent stroke after an initial embolic stroke of undetermined source and was associated with a higher risk of bleeding.
Figure 1. Cumulative Incidence of the Primary Efficacy Outcome and the Primary Safety Outcome, According to Treatment Assignment.

Panel A shows the Kaplan–Meier curves for the time to the first event of the primary efficacy outcome, defined as the recurrence of ischemic or hemorrhagic stroke or systemic embolism. Panel B shows the Kaplan–Meier curves for the time to the first primary safety outcome of major bleeding. Insets show the same data on an enlarged y axis.
RESPECT-ESUS

- Dabigatran was not superior to aspirin in preventing recurrent stroke.
- The incidence of major bleeding was not greater in the dabigatran group than in the aspirin group, but there were more clinically relevant nonmajor bleeding events in the dabigatran group.
PFO Trials, 2017

- RESPECT
- CLOSE
- REDUCE
RESPECT (extended follow up)

Original Article

Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke

Jeffrey L. Saver, M.D., John D. Carroll, M.D., David E. Thaler, M.D., Ph.D., Richard W. Smalling, M.D., Ph.D., et al., for the RESPECT Investigators

Closure group: within 300 days of stroke
- Amplatzer PFO Occluder

Medical group:
- Four groups initially allowed (ASA, warfarin, clopidogrel, and ASA+dipyridamole)

Inclusion:
- Age 18-60 years
- Cryptogenic ischemic stroke in previous 270 days
- PFO demonstrated by TEE bubble study

A Primary End-Point Events

- **Probability of Freedom from Events**
- **Years to Event**

**PFO closure group**

- Hazard ratio, 0.55 (0.31–0.999)
- P=0.046 by log-rank test

**Medical-therapy group**

**No. at Risk**
- PFO closure group: 499, 476, 464, 447, 421, 352, 262, 197, 128, 77, 41
- Medical-therapy group: 481, 433, 394, 380, 354, 282, 218, 150, 104, 59, 31
Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke

Lars Søndergaard, M.D., Scott E. Kasner, M.D., John F. Rhodes, M.D., Grethe Andersen, M.D., D.M.Sc., Helle K. Iversen, M.D., D.M.Sc., Jens E. Nielsen-Kudsk, M.D., D.M.Sc., Magnus Settergren, M.D., Ph.D., Christina Sjöstrand, M.D., Ph.D., Risto O. Roine, M.D., David Hildick-Smith, M.D., J. David Spence, M.D., and Lars Thomassen, M.D., for the Gore REDUCE Clinical Study Investigators*

- **Closure group** - Closure attempt within 90 days
  - Helex Septal Occluder device OR Cardiform Septal Occluder
  - Plavix load + a few days of Plavix, then transitioned to whatever examiner wanted.

- **Medical group**
  - Treatment chosen by local investigator
  - ASA alone (75 to 325mg once daily)
  - ASA and dipyridimole
  - Clopidogrel monotherapy (75mg once daily)

- **Inclusion**
  - 18-59 years of age
  - Cryptogenic ischemic stroke within 180 days of randomization
  - PFO with R-L shunt
<table>
<thead>
<tr>
<th>Subgroup</th>
<th>PFO Closure Group</th>
<th>Antiplatelet-Only Group</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>6/441 (1.4)</td>
<td>12/223 (5.4)</td>
<td>0.23 (0.09–0.62)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–45 yr</td>
<td>3/204 (1.5)</td>
<td>6/114 (5.3)</td>
<td>0.26 (0.07–1.04)</td>
<td>0.04</td>
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<tr>
<td>46–59 yr</td>
<td>3/237 (1.3)</td>
<td>6/109 (5.5)</td>
<td>0.21 (0.05–0.84)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3/261 (1.1)</td>
<td>8/138 (5.8)</td>
<td>0.19 (0.05–0.71)</td>
<td>0.01</td>
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</tr>
<tr>
<td>Female</td>
<td>3/180 (1.7)</td>
<td>4/85 (4.7)</td>
<td>0.31 (0.07–1.40)</td>
<td>0.11</td>
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<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
<td>1.00</td>
<td></td>
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<tr>
<td>Europe and Canada</td>
<td>3/225 (1.3)</td>
<td>6/108 (5.6)</td>
<td>0.23 (0.06–0.93)</td>
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<tr>
<td>United States</td>
<td>3/215 (1.4)</td>
<td>6/115 (5.2)</td>
<td>0.24 (0.06–0.94)</td>
<td>0.03</td>
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</tr>
<tr>
<td>Shunt size</td>
<td></td>
<td></td>
<td></td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td>1/77 (1.3)</td>
<td>2/43 (4.7)</td>
<td>0.27 (0.03–3.03)</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>Moderate-to-large</td>
<td>4/348 (1.1)</td>
<td>10/173 (5.8)</td>
<td>0.18 (0.06–0.58)</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>
Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke

• Stroke recurrence lower in PFO closure group than antiplatelet only group
• PFO closure associated with increased risk of atrial fibrillation
• One stroke avoided at 5 years for every 20 treated patients
Subgroup analysis from NAVIGATE-ESUS

- Among patients with ESUS who have PFO, anticoagulation might reduce the risk of recurrent stroke by about half.
Topics for Discussion

- Background & Stroke Basics
- Diagnosis
- Acute ischemic stroke update
- TIA/Minor stroke
- Secondary stroke prevention
- Intracranial stenosis
- Dissection
- Cryptogenic stroke
- Carotid stenosis
- Intracerebral hemorrhage
- Outpatient stroke care
The Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Study

Health and Hope for Patients at Risk for Stroke

Estimated risk of ipsilateral stroke asymptomatic carotid athero (≥50%) with modern medical therapy = 0.5-1% annually

CREST 2 - asymptomatic ≥70% carotid stenosis, compare med mgmt vs CEA or med mgmt vs CAS.
• How do we recognize **high risk** patients with asymptomatic carotid stenosis who would benefit from revascularization?
Carotid Plaque Morphology

• Data suggest that plaque morphology on imaging is a useful measure of stroke risk for patients with asymptomatic carotid stenosis.

• Carotid ulcers, echolucent plaques, intraplaque hemorrhage detected by MRI, degree of inflammation by FDG-PET
Reduced Cerebral Blood Flow Reserve

- Reduction in cerebral blood flow reserve associated with the development of ischemic stroke in patients with asymptomatic carotid stenosis in several reports
- **TCD** - measure MCA blood flow velocity in response to a vasodilatory stimulus with acetazolamide or increased CO₂
- **PET, CT/MR perfusion, nuclear medicine studies**
Asymptomatic Embolism

- Increasing evidence that asymptomatic cerebral embolism detected by TCD is associated with an ↑ risk of stroke in patients with asymptomatic carotid disease
Topics for Discussion

- Background & Stroke Basics
- Diagnosis
- Acute ischemic stroke update
- TIA/Minor stroke
- Secondary stroke prevention
- Intracranial stenosis
- Dissection
- Cryptogenic stroke
- Carotid stenosis
- Intracerebral hemorrhage
- Outpatient stroke care
Minimally Invasive Surgery for ICH
Reversal Agents

ANDEXXA is indicated for patients treated with rivaroxaban and apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.
Cerebral Amyloid Angiopathy
Topics for Discussion

• Background & Stroke Basics
• Diagnosis
• Acute ischemic stroke update
• TIA/Minor stroke
• Secondary stroke prevention

• Intracranial stenosis
• Dissection
• Cryptogenic stroke
• Carotid stenosis
• Intracerebral hemorrhage
• Outpatient stroke care
Outpatient Stroke Care

- Rehabilitation
  - Recovery time frame
- Post stroke depression
- SSRIs
- Fatigue
- Spasticity
- Risk factor screening
- Med adjustments
- Repeat imaging

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Jefferson Health.

HOME OF SIDNEY KIMMEL MEDICAL COLLEGE
Post Stroke Depression

- Prevalence is at least 20%
  - Varies over time with peak 3-6 months after stroke and subsequent decline in prevalence at one-year reaches about to 50% of initial rates
- Significant number continue to have depression 3 years out

Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial  
Lancet 2011

François Chollet, Jean Tardy, Jean-François Albucher, Claire Thalamas, Emilie Berard, Catherine Lamy, Yannick Bejot, Sandrine Deltour, Assia Jaillard, Philippe Niclot, Benoit Guillon, Thierry Moulin, Philippe Marque, Jérémie Pariente, Catherine Arnaud, Isabelle Loubinoux
Post-stroke Fatigue

- Methylphenidate
- Modafinil
- Amantadine

Post-stroke Spasticity

- Medications
- Botox with PM&R
- Neuro-technology clinic
Post Stroke Dementia

• Rapid decline in cognitive abilities
• Rare
• Similar medications
Ongoing Trials at Jefferson

• NIH StrokeNet
  • ARCADIA- cryptogenic stroke and atrial cardiopathy, is anticoagulation better than aspirin?
  • ASPIRE- restarting anticoagulation for afib after hemorrhage
  • SATURN- statins and risk of hemorrhage
• Monoclonal antibody
• Stem Cell
• Robotic arm
• https://www.jefferson.edu/academics/colleges-schools-institutes/skmc/departments/neurology/research/cerebrovascular.html
Partnership with Primary Care Provider

The American Heart Association’s “Life’s Simple 7” Steps

Get Started Now

- Get Active
- Control Cholesterol
- Eat Better
- Manage Blood Pressure
- Lose Weight
- Reduce Blood Sugar
- Stop Smoking
Questions?

Direct stroke center line (215) 955-4087
Robin.Dharia@Jefferson.edu