Stroke Care Update 2018
An evidence based approach to care standards and controversies

Ted Lowenkopf MD
Providence Comprehensive Stroke Center
Financial Disclosures

None
The most FAQs to stroke neurologists

- What is the appropriate antiplatelet management when my patient has a stroke or TIA on aspirin?

- Atrial Fibrillation:
  - What is the appropriate timing of anticoagulation after an ischemic stroke?
  - What is adequate duration of cardiac telemetry monitoring to exclude PAF?
  - When is it appropriate to offer one of the NoACs?

- What is appropriate stroke prophylaxis when TTE or TEE shows a PFO?

- What is the optimal management of asymptomatic carotid disease?

- What is the new guideline that extends the acute stroke treatment time window out to 24 hours?
Stroke Facts

- 795,000 Strokes in the US/year, one every 40 seconds
- 5th leading cause of death in the United States, 130,000 stroke deaths/year
- #1 Cause of long term adult disability, 6.5 million stroke survivors

CDC Stroke Statistics, 2015
Ischemic stroke 85%

Hemorrhagic stroke 15%

Other 5%

Cryptogenic 30%

Cardiogenic embolism 20%

Atherosclerotic cerebrovascular disease 20%

Small vessel disease “lacunes” 25%

Albers et al. *Chest* 2004; 126 (3 Suppl): 438S–512S.
The most frequent sites of arterial and cardiac abnormalities causing ischemic stroke.
“small vessel disease,”
Atherosclerotic/
lipohyalinotic
Secondary Stroke Prevention

What is the cause of the initial cerebrovascular event?

- Large- or small-vessel atherosclerosis
  - ±CEA
  - Antiplatelet therapy

- Unknown

- Cardioembolic
  - Warfarin, dabigatran, rivoroxaban, apixiban

The most FAQs to stroke neurologists

- What is the appropriate antiplatelet management when my patient has a stroke or TIA on aspirin?

- Atrial Fibrillation:
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  - What is adequate duration of cardiac telemetry monitoring to exclude PAF?
  - When is it appropriate to offer one of the NoACs?

- What is appropriate stroke prophylaxis when TTE or TEE shows a PFO?

- What is the optimal management of asymptomatic carotid disease?

- What is the new guideline that extends the acute stroke treatment time window out to 24 hours?
## Antithrombotic Therapy for Secondary Prevention of Stroke

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>WARSS</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>SPIRIT</td>
</tr>
<tr>
<td>ASA/Dipyridamole</td>
<td>WASID</td>
</tr>
<tr>
<td>Cilastazol</td>
<td>ESPRIT</td>
</tr>
<tr>
<td>Warfarin</td>
<td>ESPS 2</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>CAPRIE</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>MATCH</td>
</tr>
<tr>
<td>Apixaban</td>
<td>CHARISMA</td>
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<tr>
<td></td>
<td>PROFESS</td>
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<tr>
<td></td>
<td>CHANCE</td>
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<tr>
<td></td>
<td>Re-LY</td>
</tr>
<tr>
<td></td>
<td>Rocket-AF</td>
</tr>
<tr>
<td></td>
<td>ARISTOTLE</td>
</tr>
</tbody>
</table>
Secondary Stroke Prevention: Antiplatelet agents

- Aspirin
- Clopidogrel
- ASA/dypirimidole
Antiplatelet Therapy for stroke:

*The Stroke neurologist’s lullaby*
AHA/ASA Guideline

Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack
A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons

Walter N. Kernan, MD, Chair; Bruce Ovbiagele, MD, MSc, MAS, Vice Chair; Henry R. Black, MD; Dawn M. Bravata, MD; Marc I. Chimowitz, MBChB, FAHA; Michael D. Ezekowitz, MBChB, PhD; Margaret C. Fang, MD, MPH; Marc Fisher, MD, FAHA; Karen L. Furie, MD, MPH, FAHA; Donald V. Heck, MD; S. Claiborne (Clay) Johnston, MD, PhD; Scott E. Kasner, MD, FAHA; Steven J. Kittner, MD, MPH, FAHA; Pamela H. Mitchell, PhD, RN, FAHA; Michael W. Rich, MD; DeJuran Richardson, PhD; Lee H. Schwamm, MD, FAHA; John A. Wilson, MD; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease

Abstract—The aim of this updated guideline is to provide comprehensive and timely evidence-based recommendations on the prevention of future stroke among survivors of ischemic stroke or transient ischemic attack. The guideline is addressed to all clinicians who manage secondary prevention for these patients. Evidence-based recommendations are provided for control of risk factors, intervention for vascular obstruction, antithrombotic therapy for cardioembolism, and antiplatelet therapy for noncardioembolic stroke. Recommendations are also provided for the prevention of recurrent stroke in a variety of specific circumstances, including aortic arch atherosclerosis, arterial dissection, patent foramen ovale, hyperhomocysteinemia, hypercoagulable states, antiphospholipid antibody syndrome, sickle cell disease, cerebral venous sinus thrombosis, and pregnancy. Special sections address use of antithrombotic and antiaggregation therapy after an intracranial hemorrhage and implementation of guidelines.  

*(Stroke. 2014;45:2160-2236.)*
Does the dose of aspirin matter?

Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials

Peter M Rothwell, Nancy R Cook, J Michael Gaziano, Jacqueline F Price, Jill F F Belch, Maria Carla Roncaglioni, Takeshi Morimoto, Ziyah Mehta

Summary

Background A one-dose-fits-all approach to use of aspirin has yielded only modest benefits in long-term prevention of cardiovascular events, possibly due to underdosing in patients of large body size and excess dosing in patients of small body size, which might also affect other outcomes.

Methods Using individual patient data, we analysed the modifying effects of bodyweight (10 kg bands) and height (10 cm bands) on the effects of low doses (≤100 mg) and higher doses (300–325 mg or ≥500 mg) of aspirin in randomised trials of aspirin in primary prevention of cardiovascular events. We stratified the findings by age, sex, and vascular risk factors, and validated them in trials of aspirin in secondary prevention of stroke. Additionally, we assessed whether any weight or height dependence was evident for the effect of aspirin on 20-year risk of colorectal cancer or any in-trial cancer.

Results Among ten eligible trials of aspirin in primary prevention (including 117 279 participants), bodyweight varied four-fold and trial median weight ranged from 60·0 kg to 81·2 kg (p<0·0001). The ability of 75–100 mg aspirin to reduce cardiovascular events decreased with increasing weight (Pr interaction=0·0072), with benefit seen in people weighing 50–69 kg (hazard ratio [HR] 0·75 [95% CI 0·65–0·85]) but not in those weighing 70 kg or more (0·94 [0·83–1·06]).
**CAPRIE**

**Primary Outcome Result**

- **Patients Enrolled** (n=19,185)
- **Stroke** (n=6,431)
- **MI** (n=6,302)
- **PAD** (n=6,452)

8.7% Relative Risk Reduction (RRR) Clopidogrel vs. aspirin alone (P=0.043)

The Composite of Stroke, MI or Vascular Death

CAPRIE: Net Benefit

CV Death + MI + Stroke (primary combined endpoint)
ICH or fatal bleeding (secondary - safety)

Aspirin: n=3,198
11.1% (10.6%)
0.5%

Clopidogrel: n=3,233
10.1% (9.7%)
0.4%

Net decrease in events
Decrease in bleeding
Decrease in outcome events

CAPRIE Results by Subgroup Analysis
Aspirin vs. Clopidogrel

Relative Risk Reduction (%)

- Stroke 7.3
- MI -3.7
- PAD 23.8
- All 8.7

P = 0.26

n = 19,185
MI = myocardial infarction
PAD = peripheral arterial disease

Lancet 1996;339:1329-1339
WHAT IF I TOLD YOU

CLOPIDOGREL AND ASA ARE BETTER THAN ASA ALONE?
MATCH: Clopidogrel Plus Aspirin vs Clopidogrel Fails in Stroke

- \( n = 7,599 \)
- Stroke or TIA plus risk factor
- Clopidogrel + ASA vs clopidogrel

Results

- No difference in stroke/MI/death or stroke outcomes
- Major bleeds and life-threatening bleeds significantly higher with combination treatment

MATCH: Net Benefit
Combined Endpoint vs. Serious Bleeding

- Stroke + MI + CV death (primary combined endpoint)
- Life-threatening bleeding (secondary - safety)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events/1.5 yr (%)</th>
<th>Clopidogrel</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel + Placebo</td>
<td>13.3%</td>
<td>12.0%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Clopidogrel + ASA</td>
<td>13.8%</td>
<td>11.2%</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

Net increase in events

<table>
<thead>
<tr>
<th><strong>Study design</strong></th>
<th>768 clinical centers in 32 countries; randomized, blinded</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study population</strong></td>
<td>15,603 patients &gt; 45 years (median age 64 years) with cardiovascular disease or multiple risk factors</td>
</tr>
<tr>
<td><strong>Study drugs</strong></td>
<td>Clopidogrel (75 mg/day)+ low dose ASA (75-162 mg/day) vs low-dose aspirin</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>Composite outcome cluster of ischemic stroke, MI, vascular death</td>
</tr>
<tr>
<td><strong>Treatment duration</strong></td>
<td>Average patient follow-up 28 months</td>
</tr>
</tbody>
</table>
CHARISMA: Net Benefit/Risk

1 event avoided/1,000 treated/2.3 years

- **ASA + Placebo**
  - n = 7,801
  - **8.6% Stroke + MI + CV death**
    (primary combined endpoint)
  - **1.3% Severe/fatal bleeding**

- **Clopidogrel + ASA**
  - n = 7,802
  - **8.5% Stroke + MI + CV death**
  - **1.7% Severe/fatal bleeding**

- Increase in bleeding
- Decrease in outcome events

# European Stroke Prevention Study 2 (ESPS 2): Trial Design


<table>
<thead>
<tr>
<th>Study design</th>
<th>59 clinical centers in 13 European countries; randomized, doubleblind, placebocontrolled with a 2 x 2 factorial design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study population</td>
<td>6,602 patients &gt;18 yr (mean age 66.7 yr) with recent cerebrovascular episode (within 90 days of study entry)</td>
</tr>
<tr>
<td>Study drugs</td>
<td>ASA/ERDP (25 mg ASA/200 mg ER-DP bid); ER-DP (200 mg bid); ASA (25 mg bid); placebo</td>
</tr>
<tr>
<td>1º endpoint</td>
<td>Stroke, death, and stroke or death together</td>
</tr>
<tr>
<td>2º endpoint</td>
<td>TIA and other vascular events</td>
</tr>
<tr>
<td>Treatment duration</td>
<td>Treatment period 2 yr; patient follow-up 2 yr</td>
</tr>
</tbody>
</table>
26 events avoided/1000 treated/2 yr


**ESPS 2: Net Benefit**

- **Aspirin**
  - n=1,649
  - Stroke: 12.5%
  - Serious bleeding (severe or fatal): 1.2%
  - Net decrease in events: 13.7%

- **Aspirin/ER-DP**
  - n=1,650
  - Stroke: 9.5%
  - Serious bleeding (severe or fatal): 1.6%
  - Net decrease in combined endpoint: 11.1%

Net decrease in events: ↓
Increase in bleeding: ↑
Decrease in combined endpoint: ↓
Prevention Regimen For Effectively avoiding Second Strokes – The PRoFESS Trial
### Profess Study Design

<table>
<thead>
<tr>
<th>Telmisartan</th>
<th>Telmisartan placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER-DP+ASA</td>
<td>Clopidogrel*</td>
</tr>
<tr>
<td>ER-DP+ASA + Telmisartan</td>
<td>Clopidogrel + Telmisartan</td>
</tr>
<tr>
<td>ER-DP+ASA + Telmisartan placebo</td>
<td>Clopidogrel + Telmisartan placebo</td>
</tr>
</tbody>
</table>

**20,332 pts**
PRoFESS

- 20,333 patients
- Mean duration 2.4 years
- Primary outcome: first recurrence of stroke
- Secondary outcome: composite of stroke, MI, death from vascular cause
- Ultimately designed to demonstrate non-inferiority
- Inclusion: recent stroke, age >50,
Primary Outcome: Stroke Recurrence

<table>
<thead>
<tr>
<th></th>
<th>ASA+ER-DP</th>
<th>Clopidogrel</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count (%</td>
<td>916 (9.0%)</td>
<td>898 (8.8%)</td>
<td>1.01</td>
<td>0.92, 1.11</td>
<td>0.783</td>
</tr>
</tbody>
</table>

* Covariates in cox model are age, baseline ACE-inhibitor use, Modified Rankin, and baseline diabetes status.

10/05/2008
Characterization of First Recurrent Stroke

- **Hemorrhagic**
  - Clopidogrel: 898 (8.8%)
  - ASA+ER-DP: 915 (9.0%)
  - Total: 17 strokes

- **Ischemic**
  - Clopidogrel: 805 (7.9%)
  - ASA+ER-DP: 780 (7.7%)
  - Total: 25 Ischemic strokes

- **Other/Unk**
  - Clopidogrel: 48 (0.5%)
  - ASA+ER-DP: 52 (0.5%)

- **Comparison**
  - Clopidogrel: 38 Hemorrhagic strokes
  - ASA+ER-DP: 83 (0.8%)
Secondary Outcome: Stroke, MI, Vascular Death

Covariates in cox model are age, baseline ACE-inhibitor use, Modified Rankin, and baseline diabetes status.

<table>
<thead>
<tr>
<th></th>
<th>ASA+ER-DP</th>
<th>Clopidogrel</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at risk:</td>
<td>ASA+ER-DP</td>
<td>Clopidogrel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA+ER-DP</td>
<td>10181</td>
<td>10151</td>
<td>1333 (13.1%)</td>
<td>1333 (13.1%)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

* Covariates in cox model are age, baseline ACE-inhibitor use, Modified Rankin, and baseline diabetes status.
Before PRoFESS

A Not Including Data from the PRoFESS Trial

Aspirin

Relative risk, 0.79
(95% CI, 0.67 to 0.92);
P=0.003

Relative risk, 0.92
(95% CI, 0.80 to 1.07);
P=0.27

Aspirin–ERDP

Indirect relative risk, 0.86
(95% CI, 0.69 to 1.06);
P=0.16

Clopidogrel

Kent, DM Thaler, DE *NEJM* 359;12 2008
After PRoFESS

B Including Data from the PRoFESS Trial

Relative risk, 0.83
(95% CI, 0.68 to 1.02);
P=0.08

Aspirin

Relative risk, 0.87
(95% CI, 0.71 to 1.07);
P=0.19

Aspirin–ERDP

Relative risk, 0.96
(95% CI, 0.78 to 1.18);
P=0.70

Clopidogrel

From PRoFESS Trial
Direct relative risk, 1.02
(95% CI, 0.93 to 1.11);
P=0.71

Kent, DM Thaler, DE NEJM 359;12 2008
Short-term Risk Reduction from DAPT?

- POINT
**Table 2. Efficacy and Safety Outcomes.**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Clopidogrel plus Aspirin (N=2432)</th>
<th>Aspirin (N=2449)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary efficacy outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite of ischemic stroke, myocardial infarction, or death from ischemic vascular causes</td>
<td>121 (5.0)</td>
<td>160 (6.5)</td>
<td>0.75 (0.59–0.95)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Secondary efficacy outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>112 (4.6)</td>
<td>155 (6.3)</td>
<td>0.72 (0.56–0.92)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>10 (0.4)</td>
<td>7 (0.3)</td>
<td>1.44 (0.55–3.78)</td>
<td>0.46*</td>
</tr>
<tr>
<td>Death from ischemic vascular causes</td>
<td>6 (0.2)</td>
<td>4 (0.2)</td>
<td>1.51 (0.43–5.35)</td>
<td>0.52*</td>
</tr>
<tr>
<td>Ischemic or hemorrhagic stroke</td>
<td>116 (4.8)</td>
<td>156 (6.4)</td>
<td>0.74 (0.58–0.94)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Composite of ischemic stroke, myocardial infarction, death from ischemic vascular causes, or major hemorrhage</td>
<td>141 (5.8)</td>
<td>167 (6.8)</td>
<td>0.84 (0.67–1.05)</td>
<td>0.13*</td>
</tr>
<tr>
<td><strong>Primary safety outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major hemorrhage</td>
<td>23 (0.9)</td>
<td>10 (0.4)</td>
<td>2.32 (1.10–4.87)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
POINT

B Primary Safety Outcome: Major Hemorrhage

<table>
<thead>
<tr>
<th></th>
<th>No. of Patients</th>
<th>No. with Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>2449</td>
<td>10</td>
</tr>
<tr>
<td>Clopidogrel plus Aspirin</td>
<td>2432</td>
<td>23</td>
</tr>
</tbody>
</table>

Hazard ratio, 2.32 (95% CI, 1.10–4.87)  
P=0.02

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Aspirin</th>
<th>Clopidogrel plus aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at Risk</td>
<td>2449</td>
<td>2432</td>
</tr>
<tr>
<td></td>
<td>2372</td>
<td>2336</td>
</tr>
<tr>
<td></td>
<td>2271</td>
<td>2256</td>
</tr>
<tr>
<td></td>
<td>2230</td>
<td>2192</td>
</tr>
<tr>
<td></td>
<td>1448</td>
<td>1505</td>
</tr>
</tbody>
</table>
Conclusion?

- In the case of PRoFESS and the tangle of related trials, enlightenment might be expressed simply, as a haiku: “For stroke prevention, / use an antiplatelet drug. / Treat hypertension.”

Kent, DM  Thaler, DE  *NEJM* 359;12 2008
The most FAQs to stroke neurologists

- What is the appropriate antiplatelet management when my patient has a stroke or TIA on aspirin?

- Atrial Fibrillation:
  - What is the appropriate timing of anticoagulation after an ischemic stroke?
  - What is adequate duration of monitoring to exclude PAF?
  - When is it appropriate to offer one of the NoACs?
  - Is it ever appropriate to anticoagulate after ICH (intracerebral hemorrhage)?

- What is appropriate stroke prophylaxis when TTE or TEE shows a PFO?

- What is the optimal management of asymptomatic carotid disease?

- My patient had a TIA/stroke, what is the work up?
<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Stroke risk per year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C</strong> Congestive Heart Failure</td>
<td>+1 point</td>
</tr>
<tr>
<td><strong>H</strong> Hypertension</td>
<td>+1 point</td>
</tr>
<tr>
<td><strong>A&lt;sub&gt;2&lt;/sub&gt;</strong> Age ≥75</td>
<td>+2 point</td>
</tr>
<tr>
<td><strong>D</strong> Diabetes</td>
<td>+1 point</td>
</tr>
<tr>
<td><strong>S&lt;sub&gt;2&lt;/sub&gt;</strong> Stroke/TIA History</td>
<td>+2 point</td>
</tr>
<tr>
<td><strong>V</strong> Vascular Disease</td>
<td>+1 point</td>
</tr>
<tr>
<td><strong>A</strong> Age 65-74</td>
<td>+1 point</td>
</tr>
<tr>
<td><strong>S</strong> Sex (Female)</td>
<td>+1 point</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SCORE</th>
<th>% RATE PER YEAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>1</td>
<td>1.3%</td>
</tr>
<tr>
<td>2</td>
<td>2.2%</td>
</tr>
<tr>
<td>3</td>
<td>3.2%</td>
</tr>
<tr>
<td>4</td>
<td>4.0%</td>
</tr>
<tr>
<td>5</td>
<td>6.7%</td>
</tr>
<tr>
<td>6</td>
<td>9.8%</td>
</tr>
<tr>
<td>7</td>
<td>9.6%</td>
</tr>
<tr>
<td>8</td>
<td>6.7%</td>
</tr>
<tr>
<td>9</td>
<td>15.2%</td>
</tr>
</tbody>
</table>

Capturing PAF

- 2/3 of cases of a fibrillation are paroxysmal\(^1\), same risk of stroke.
- The longer duration of monitoring the more likely that you will detect PAF.

\(^1\) Circulation. 2006;114:119–125.
Atrial Fibrillation Burden: Moving Beyond Atrial Fibrillation as a Binary Entity

A Scientific Statement From the American Heart Association

ABSTRACT: Our understanding of the risk factors and complications of atrial fibrillation (AF) is based mostly on studies that have evaluated AF in a binary fashion (present or absent) and have not investigated AF burden. This scientific statement discusses the published literature and knowledge gaps related to methods of defining and measuring AF burden, the relationship of AF burden to cardiovascular and neurological outcomes, and the effect of lifestyle and risk factor modification on AF burden. Many studies examine outcomes by AF burden classified by AF type (paroxysmal versus nonparoxysmal); however, quantitatively, AF burden can be defined by longest duration, number of AF episodes during a monitoring period, and the proportion of time an individual is in AF during a monitoring period (expressed as a percentage). Current guidelines make identical recommendations for anticoagulation regardless of AF pattern or burden; however, a review of recent evidence suggests that higher AF burden is associated with higher risk of stroke. It is unclear whether the risk increases continuously or whether a threshold exists; if a threshold exists, it has not been defined. Higher burden of AF is also associated with higher prevalence and incidence of heart failure and higher risk of mortality, but not necessarily lower quality of life. A structured and comprehensive risk factor management program targeting risk factors, weight loss, and maintenance of a healthy weight appears to be effective in reducing AF burden. Despite this growing understanding of AF burden, research is needed into validation of definitions and measures of AF burden, determination of the threshold of AF burden that results in an increased risk of stroke that warrants anticoagulation, and discovery of the mechanisms underlying the weak temporal correlations of AF and stroke. Moreover, developments in monitoring technologies will likely change the landscape of long-term AF monitoring and could allow better definition of the significance of changes in AF burden over time.

Key Words: Atrial Fibrillation • Lifestyle • Risk factors • Stroke

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http://circ.ahajournals.org

Circulation. 2018;137:e623–e644. DOI: 10.1161/CIR.0000000000000568

May 15, 2018 e623

- Number of episodes
- Longest duration
- Percent of time
Methods of capturing PAF

Non-Invasive

- EKG
- MCOT™
- ZIO™

Invasive

- LYNC™
- Pacemaker
- Defibrillator
Cardiac tele monitoring for afib

- PAF detection over average hosp LOS: ~3%
- 48 holter 2-3%
- 30 day monitor 11-16 %
- 6 month monitor 22%
- 12 month 25%
- 36 months 30%

Presented ISC, San Diego 2/2014
Questions that remain....

- What duration of monitoring is enough?

- What duration or frequency of afib on monitor is enough to increase stroke risk and merit anticoagulation?

- Another approach: NAVIGATE-ESUS, RE-SPECT ESUS,
Comparison of Novel Anticoagulants to warfarin for stroke prophylaxis and safety

<table>
<thead>
<tr>
<th></th>
<th>STROKE</th>
<th>BLEEDING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Better</td>
<td>Equal</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Equal</td>
<td>Equal</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Better</td>
<td>Better</td>
</tr>
</tbody>
</table>
Patients to consider for NoAcs

- Intolerant of warfarin
- Unstable INR
- Unable to get INR
- Offer to new patients
- Stable patients?
Timing of anticoagulation after stroke with atrial fibrillation

76 year-old man with atrial fibrillation presents with 8 hours of left sided weakness and slurred speech.
Timing of anticoagulation after stroke with atrial fibrillation

- What is the risk of recurrent stroke off anticoagulation?
- What is the risk of hemorrhagic transformation on anticoagulation?
Timing of anticoagulation after stroke with atrial fibrillation

- 4.9% 14 day recurrence\(^1\)

- Risk of hemorrhagic complication is linked to \(^2\):
  - Size of stroke
  - Timing of stroke
  - Degree of anticoagulation
  - Patient age
  - History of diabetes
  - History of hypertension
  - Presence of ‘microvascular’ changes on CT/MRI

1 Stroke. 2001; 32: 2333-2337
Timing of anticoagulation after stroke with atrial fibrillation

For most patients with a stroke or TIA in the setting of AF, it is reasonable to initiate oral anticoagulation within 14 days after the onset of neurological symptoms (Class IIa; Level of Evidence B). (New recommendation)

In the presence of high risk for hemorrhagic conversion (ie, large infarct, hemorrhagic transformation on initial imaging, uncontrolled hypertension, or hemorrhage tendency), it is reasonable to delay initiation of oral anticoagulation beyond 14 days (Class IIa; Level of Evidence B). (New recommendation)
The most FAQs to stroke neurologists

- What is the appropriate antiplatelet management when my patient has a stroke or TIA on aspirin?

- Atrial Fibrillation:
  - What is the appropriate timing of anticoagulation after an ischemic stroke?
  - What is adequate duration of monitoring to exclude PAF?
  - When is it appropriate to offer one of the NoACs?
  - Is it ever appropriate to anticoagulate after ICH (intracerebral hemorrhage)?

- What is appropriate stroke prophylaxis when TTE or TEE shows a PFO?

- What is the optimal management of asymptomatic carotid disease?

- My patient had a TIA/stroke, what is the work up?
Incidence of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts
Rate of recurrent strokes under medical treatment in patients with patent foramen ovale and prior cryptogenic stroke is very low - about 2% per year (expressed as events/100 person-years of follow-up).

(Kent et al. Neurology 2011;77:301-302)
PFO and Stroke

1. Is PFO Causally Related to Stroke?

2. What is the best medical management for secondary stroke prevention in patients with PFO?

3. Is there a role for mechanical PFO closure for secondary stroke prevention in patients with PFO?
PFO Stroke Pathophysiology

Paradoxical embolism?
SPECIAL ARTICLE
Hospital Readmission Risk — Isolating Hospital Effects from Patient Effects
H.M. Knudtzol and Others

REVIEW ARTICLE
Recent Developments in Radiotherapy
D. E. Cahn

IMAGES IN CLINICAL MEDICINE
Marfan’s Syndrome with Ectopia Lentis
J. Sridhar and J. S. Chang
Free Full Text

Indodonesia
D. Dusil and A. J. Tijj
Free Full Text

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL
Case 28-2017 — A 13-Month-Old Girl with Pneumonia and a 33-Year-Old Woman with Hip Pain
S.M. Holland, V.M. Pierce, R. Shalem, K. Giomski, and J.R. Farmer

EDITORIAL
Tipping Point for Patent Foramen Ovale Closure
A.H. Hopper

CLINICAL IMPLICATIONS OF BASIC RESEARCH
Waving Hello to Noninvasive Deep-Brain Stimulation
A.M. Lozano

CORRESPONDENCE
Vaccination Rates among Younger Siblings of Children with Autism
Free Full Text
CLOSE

- Primary Endpoint: stroke
- Number of patients: 663
- Key Inclusion: 16-60, PFO with > 30 bubbles and ASA of >10 mm
- Key Exclusion: stroke of know etiology
- Medical Therapy: ASA vs Warfarin
- Mean follow-up: 5.3 years
The Kaplan-Meier survival analysis shows the probability of event-free survival over time for patients in the PFO closure group and the antiplatelet-only group. The graph indicates a significant hazard ratio, 0.03 (95% CI, 0 to 0.26), with a P-value <0.001 by log-rank test.

**No. at Risk**

- **PFO closure group**: 238, 238, 232, 200, 179, 141, 99, 64, 20, 0, 0
- **Antiplatelet-only group**: 235, 229, 223, 198, 160, 130, 96, 55, 19, 0, 0
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Randomization Groups 1 and 2</th>
<th>Randomization Groups 1 and 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PFO Closure Group (N = 238)</td>
<td>Antplatelet-Only Group (N = 235)</td>
</tr>
<tr>
<td></td>
<td>Hazard Ratio (95% CI)†</td>
<td>P Value</td>
</tr>
<tr>
<td></td>
<td>0.03 (0.00-0.26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>0.04 (0.00-0.27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PRIMARY EFFICACY OUTCOME</td>
<td>0.44 (0.11-1.48)</td>
<td>0.37 (0.07-1.38)</td>
</tr>
<tr>
<td>Stroke in the intention-to-treat population — no. of patients</td>
<td>14§</td>
<td>7§</td>
</tr>
<tr>
<td>Stroke in the per-protocol population — no./total no. of patients</td>
<td>14/223§</td>
<td>7/164§</td>
</tr>
<tr>
<td>SECONDARY EFFICACY OUTCOMES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disabling stroke**</td>
<td>0.33 (0.03-6.18)</td>
<td>0.96 (0.08-11.35)</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Ischemic stroke, transient ischemic attack, or systemic embolism</td>
<td>0.39 (0.16-0.82)</td>
<td>0.64 (0.26-1.50)</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>0.97 (0.37-2.56)</td>
<td>0.80 (0.25-2.52)</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Success of device implantation — no./total no. (%)†††</td>
<td>234/235 (96.9)</td>
<td>NA</td>
</tr>
<tr>
<td>Success of PFO closure — no./total no. (%)§§§</td>
<td>202/228 (88.6)</td>
<td>NA</td>
</tr>
</tbody>
</table>

*NA denotes not applicable. The intention-to-treat cohort included all patients who were randomly assigned to a treatment. The per-protocol cohort included patients who received the randomly assigned treatment, adhered to the protocol-mandated medical treatment until the end of the trial, and did not have a major protocol violation.
†The hazard ratio was calculated for the PFO closure group as compared with the antplatelet-only group.
‡The hazard ratio was calculated for the anticoagulant group as compared with the antplatelet-only group. Statistical significance was not analyzed because the study was not adequately powered to compare outcomes in these groups.
§No patient had an alternative explanation for recurrent stroke.
¶One patient had an alternative cause of stroke (aneurysmal subarachnoid hemorrhage complicated by vasospasm and ischemic strokes).
**Secondary efficacy outcomes were analyzed in the intention-to-treat cohort.
††Disabling stroke was defined as a modified Rankin scale score of 3 or higher.
†††The one death was due to pancreatic cancer.
§§§Success of device implantation was defined as deployment of the device in the appropriate place and removal of the placement system.
§§Success of PFO closure was defined as successful implantation with no complication before the patient’s discharge and no or minimal residual shunt.
<table>
<thead>
<tr>
<th>Complication or Event</th>
<th>Randomization Groups 1 and 2</th>
<th>Randomization Groups 1 and 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PFO Closure Group (N=238)</td>
<td>Antiplatelet-Only Group (N=235)</td>
<td>P Value</td>
</tr>
<tr>
<td></td>
<td>no. of patients (%)</td>
<td>no. of patients (%)</td>
<td></td>
</tr>
<tr>
<td>Major or fatal device-related or procedure-</td>
<td>14 (5.9)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>related complication†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major or fatal bleeding complication</td>
<td>2 (0.8)</td>
<td>5 (2.1)</td>
<td>0.28</td>
</tr>
<tr>
<td>Atrial fibrillation or flutter‡</td>
<td>11 (4.6)§</td>
<td>2 (0.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>At least one serious adverse event</td>
<td>85 (35.7)</td>
<td>78 (33.2)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

* Definitions of major or fatal device-related or procedure-related complications, definitions of major or fatal bleeding complications, and a full list of serious adverse events are provided in the Supplementary Appendix.
† Major or fatal device-related or procedure-related complications in the PFO closure group are listed for those that occurred within 30 days after the procedure and included atrial fibrillation (9 patients), atrial flutter (1 patient), supraventricular tachycardia (2 patients), air embolism (1 patient), and hyperthermia resulting in prolongation of hospitalization (1 patient).
‡ Atrial fibrillation or flutter was classified as cases that required treatment for more than 1 month.
§ In 10 patients, atrial fibrillation or flutter occurred within 30 days after the procedure.
¶ The one death was due to pancreatic cancer.
Study Design: 2:1 randomization to PFO closure vs antiplatelet therapy
Primary Endpoint: EP
24 month event free and 24 month silent and clinical stroke
Number of patients: 644
Key Inclusion: Cryptogenic stroke, 18-59
PFO Closure vs Antiplatelet
Median follow-up: 3.2 years
Hazard ratio for recurrent stroke, 0.23 (95% CI, 0.09–0.62) P=0.002 by log-rank test

<table>
<thead>
<tr>
<th>Follow-up (mo)</th>
<th>0.00</th>
<th>0.10</th>
<th>0.20</th>
<th>0.30</th>
<th>0.40</th>
<th>0.50</th>
<th>0.60</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at Risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFO closure group</td>
<td>441</td>
<td>422</td>
<td>417</td>
<td>398</td>
<td>278</td>
<td>182</td>
<td>102</td>
</tr>
<tr>
<td>Antiplatelet-only group</td>
<td>223</td>
<td>202</td>
<td>194</td>
<td>173</td>
<td>116</td>
<td>78</td>
<td>30</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>PFO Closure Group (N = 441)</td>
<td>Antiplatelet-Only Group (N = 223)</td>
<td>P Value*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>----------------------------</td>
<td>----------------------------------</td>
<td>----------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>102 (23.1)</td>
<td>62 (27.8)</td>
<td>0.22</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Device related</td>
<td>6 (1.4)</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedure related</td>
<td>11 (2.5)</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death†</td>
<td>2 (0.5)</td>
<td>0</td>
<td>0.55</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious bleeding adverse event</td>
<td>8 (1.8)</td>
<td>6 (2.7)</td>
<td>0.57</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedure associated‡</td>
<td>4 (0.9)</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other‡</td>
<td>4 (0.9)</td>
<td>6 (2.7)</td>
<td>0.09</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any atrial fibrillation or flutter</td>
<td>29 (6.6)</td>
<td>1 (0.4)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious atrial fibrillation or flutter¶</td>
<td>10 (2.3)</td>
<td>1 (0.4)</td>
<td>0.11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious device-related adverse event∥</td>
<td>6 (1.4)</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Device dislocation</td>
<td>3 (0.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Device-related thrombosis</td>
<td>2 (0.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic dissection</td>
<td>1 (0.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any deep-vein thrombosis or pulmonary embolism</td>
<td>3 (0.7)</td>
<td>2 (0.9)</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
RESPECT

- Study Design: PFO closure vs medical therapy
- Primary Endpoint: ischemic stroke
- Number of patients: 980
- Key Inclusion: 18-60, stroke within 6 months
- Key Exclusion: stroke of known etiology
- Mean follow-up: 5.9 years
<table>
<thead>
<tr>
<th>End Point</th>
<th>PFO Closure Group (N = 499)</th>
<th>Medical-Therapy Group (N = 481)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with Event no. (%)</td>
<td>Event Rate per 100 Patient-Yr</td>
<td>Patients with Event no. (%)</td>
<td>Event Rate per 100 Patient-Yr</td>
</tr>
<tr>
<td>Recurrent ischemic stroke</td>
<td>18 (3.6)</td>
<td>0.58</td>
<td>28 (5.8)</td>
<td>1.07</td>
</tr>
<tr>
<td>Recurrent ischemic stroke of undetermined cause as adjudicated with the use of ASCOD</td>
<td>10 (2.0)</td>
<td>0.32</td>
<td>23 (4.8)</td>
<td>0.86</td>
</tr>
<tr>
<td>Recurrent cryptogenic ischemic stroke as adjudicated with the use of TOAST</td>
<td>1 (0.2)</td>
<td>0.03</td>
<td>11 (2.3)</td>
<td>0.41</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>17 (3.4)</td>
<td>0.54</td>
<td>23 (4.8)</td>
<td>0.86</td>
</tr>
</tbody>
</table>

* The end points shown are the first such event that occurred in a patient, not second or later recurrences. ASCOD denotes atherosclerosis (A), small-vessel disease (S), cardiac pathology (C), other causes (O), dissection (D), and TOAST Trial of ORG 10172 in Acute Stroke Treatment.13
PFO and stroke: Take homes

- In recent studies PFO closure significantly reduced stroke incidence in young patients with cryptogenic stroke when compared to antiplatelet therapy; no benefit when compared to anticoagulation

- NNT to prevent one stroke at 5 years: 20-28

- ~ 5% risk of atrial fibrillation from procedure

- In patients with cryptogenic stroke and PFO, closure of PFO can be offered in patients < 60 years old after thorough work-up including TEE, cerebrovascular imaging, and hypercoaguable studies
The most FAQs to stroke neurologists

- What is the appropriate antiplatelet management when my patient has a stroke or TIA on aspirin?

- My patient had a TIA/stroke, what is the work up?

- Atrial Fibrillation:
  - What is the appropriate timing of anticoagulation after an ischemic stroke?
  - What is adequate duration of monitoring to exclude PAF?
  - When is it appropriate to offer one of the NoACs?
  - Is it ever appropriate to anticoagulate after ICH (intracerebral hemorrhage)?

- What is appropriate stroke prophylaxis when TTE or TEE shows a PFO?

- What is the optimal management of carotid disease?
Two-year risk of stroke with *symptomatic* carotid disease

<table>
<thead>
<tr>
<th>Stenosis</th>
<th>NASCET</th>
<th>ECST</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-69%</td>
<td>14.6%</td>
<td>9.7%</td>
</tr>
<tr>
<td>70-99%</td>
<td>24.5%</td>
<td>19.9%</td>
</tr>
</tbody>
</table>

Barnett HM *et al* *CMAJ* 166: 1169-79 2002
Carotid endarterectomy: Controversies

- Is carotid ultrasound an adequate measure of stenosis? *Sometimes*
- Is there an optimal timing of surgery? *Yes*
- What is the best management of asymptomatic disease?
Timing of CEA after stroke/TIA: NASCET and ECST data

<table>
<thead>
<tr>
<th>Time since last event (weeks)</th>
<th>Surgical Events</th>
<th>Medical Events</th>
<th>ARR (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2</td>
<td>13/112</td>
<td>26/75</td>
<td>24.7</td>
<td>12.3–37.1</td>
</tr>
<tr>
<td></td>
<td>27/213</td>
<td>62/224</td>
<td>15.9</td>
<td>8.3–23.5</td>
</tr>
<tr>
<td></td>
<td>40/325</td>
<td>88/299</td>
<td>18.5</td>
<td>12.1–24.9</td>
</tr>
<tr>
<td>2–4</td>
<td>17/136</td>
<td>13/81</td>
<td>4.4</td>
<td>-5.5–14.2</td>
</tr>
<tr>
<td></td>
<td>14/132</td>
<td>31/134</td>
<td>13.1</td>
<td>4.0–22.2</td>
</tr>
<tr>
<td></td>
<td>31/268</td>
<td>44/215</td>
<td>9.8</td>
<td>3.0–16.5</td>
</tr>
<tr>
<td>4–12</td>
<td>29/271</td>
<td>31/216</td>
<td>4.1</td>
<td>-2.0–10.2</td>
</tr>
<tr>
<td></td>
<td>34/289</td>
<td>50/282</td>
<td>6.4</td>
<td>0.4–12.5</td>
</tr>
<tr>
<td></td>
<td>63/560</td>
<td>81/498</td>
<td>5.5</td>
<td>1.2–9.8</td>
</tr>
</tbody>
</table>

Asymptomatic Carotid Stenosis

ACAS: Prevention of ipsilateral stroke
Surgery vs medical therapy at 5 yrs

<table>
<thead>
<tr>
<th>Stenosis</th>
<th>Abs.RR%</th>
<th>RRR%</th>
<th>NNT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>60-99%</td>
<td>5.9</td>
<td>53</td>
<td>17</td>
<td>0.004</td>
</tr>
</tbody>
</table>

JAMA 273: 1421-28  1995
ACAS: 4 years to benefit
Management of asymptomatic carotid stenosis

- 3% per year stroke risk with 80-99% (previous trials)
- 5% per year with 90-99% (previous trials)
- Recent data shows stroke risk of 0.5% to 1% per year when carotid stenosis > 50%.
- A recent meta analysis showed decrease stroke rates 2.83% before 2000 to 1.13% per year after 2000.

Asymptomatic carotid stenosis: What’s Next?

The Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Study
Health and Hope for Patients at Risk for Stroke

Please refer patient with greater than 70% stenosis by ultrasound
503-216-1051 or
Theodore.Lowenkopf@providence.org
Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging


ABSTRACT

BACKGROUND

Thrombectomy is currently recommended for eligible patients with stroke who are treated within 6 hours after the onset of symptoms.
Conclusions

- **Antiplatelet Therapy After Stroke:**
  - Choose one, no evidence that increasing aspirin helps, treat risk factors
  - Dual antiplatelet therapy started immediately after a small stroke or TIA

- **Atrial Fibrillation:** Monitor for ~ 30 days, NoACs are good alternatives to warfarin, wait ~ 14 days to anticoagulate after significant stroke

- **Asymptomatic Carotid Disease:** Clinical equipoise on CEA/CAS, please refer to trial
Conclusions

- **Patent Foramen Ovale and Stroke:** PFO closure can be considered in patients under 60 after complete work up, NNT 20-28, ~5% risk of Afib

- **Acute Stroke Treatment New Time Window:**
  In patient’s with large vessel occlusion and favorable prefusion profiles stroke can be treated out to 24 hours after last known normal
<table>
<thead>
<tr>
<th>3.7. Mechanical Thrombectomy (Continued)</th>
<th>COR</th>
<th>LOE</th>
<th>New, Revised, or Unchanged</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. In selected patients with AIS within 6 to 16 hours of last known normal who have LVO in the anterior circulation and meet other DAWN or DEFUSE 3 eligibility criteria, mechanical thrombectomy is recommended.</td>
<td>I</td>
<td>A</td>
<td>New recommendation.</td>
</tr>
</tbody>
</table>