Ischemic Stroke: Acute Treatment and Secondary Prevention

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Director, Stroke Center Medical Quality
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Director, UCLA TeleStroke Program
Disclosures

• Off-label and investigational products and treatments will be discussed as part of clinical trials

• Scientific Advisory Board, AstraZeneca
Learning Objectives

• Discuss guideline based acute ischemic stroke management

• Identify opportunities to reduce recurrent ischemic strokes

• Describe guidelines-based recurrent ischemic stroke prevention strategies
Societal Impact

- Leading cause of adult disability in US
- 5th leading cause of death
- 2nd leading cause of dementia
- ~800,000 new strokes each year
- $70 billion per year in the United States
Aging and Ischemic Stroke

- 75% percent of strokes occur in people >65
- Estimates suggest the chance of having a stroke doubles every decade after 55
How Bad is a Major Stroke?

Worse than death

Equivalent to being well

Equivalent to death
Transient Ischemic Attacks (TIA)

• Traditional time definition: Duration < 24 hours

• New tissue definition (2013)
  – Transient focal ischemia + deficits <24hrs without evidence of brain infarction by imaging or pathology
  – ~40% of time-defined TIA patients show DWI MR abnormality

• May occur with any cause of ischemic stroke
  – Large artery athero > lacune > cardioembolic

• After TIA, ten times the risk of ischemic stroke
  – Risk highest in first 3 months following TIA
  – 35% stroke risk within 3-5 years after TIA

ABCDS Score – 7 Days Stroke Risk

<table>
<thead>
<tr>
<th>Points</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60</td>
<td>1</td>
</tr>
<tr>
<td>Blood pressure ≥ 140/90</td>
<td>1</td>
</tr>
<tr>
<td>Clinical features</td>
<td></td>
</tr>
<tr>
<td>Unilateral weakness</td>
<td>2</td>
</tr>
<tr>
<td>Speech disturbance w/o weakness</td>
<td>1</td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td></td>
</tr>
<tr>
<td>&gt; 10 min &lt; 59 min</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 60 min</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
</tr>
</tbody>
</table>

Risk: Score < 5 = 4%  Score of 5 = 16%  Score ≥ 6 = 35%

Score 6-7: 8.1 percent (high risk)
Score 4-5: 4.1 percent (moderate risk)
Score 0-3: 1.0 percent (low risk)
Stroke Subtypes

Kleindorfer et al. 2021 Guidelines for the prevention of Stroke
Stroke Risk Factors

Non-Modifiable Risk Factors
- Ethnicity
- Age
- Gender
- Family History

Modifiable Risk Factors
- Hypertension
- Atrial Fibrillation
- Lipid Levels
- Smoking
- Obesity
- Unhealthy Diet
- Psychosocial Factors
- Low Physical Activity
- Heavy Alcohol Intake
- Diabetes

Sacco, American Heart Association, 1998
Acute Interventions


William J. Powers, Alejandro A. Rabinstein, Teri Ackerson, Opeolu M. Adeoye, Nicholas G. Bambrickidis, Kyra Becker, Joes Biller, Michael Brown, Bart M. Demaerschalk, Brian Hoh, Edward C. Jauch, Chelsea S. Kidwell, Thabile M. Leslie-Mazwi, Bruce Ovbiagele, Phillip A. Scott, Kevin N. Sheth, Andrew M. Sotherland, Deborah V. Summers, David L. Tirschwell, ... See all authors

Treatment of Acute Ischemic Stroke = solving a Simple Plumbing Problem

An ischemic stroke occurs when a blood vessel supplying the brain becomes blocked, as by a clot.

Some Cells May Be Saved!

- When an artery is blocked (occlusion) and brain cells do not receive the oxygen they need, brain cells in the infarct (ischemic core of the stroke) may be damaged beyond recovery.

- The brain cells in the penumbra (the area that surrounds the ischemic core) still receive some blood.

- Cells in the penumbra have the potential to recover under the right conditions.

Jung S, Liebeskind D. Relevance of the cerebral collateral circulation in ischaemic stroke: time is brain, but collaterals set the pace. Swiss Med Wkly. 2017;147:w14538
In a typical acute ischemic stroke, every minute the brain loses

- 1.9 million neurons
- 14 billion synapses
- 7.5 miles myelinated fibers
Stroke- The Golden Hour

- Narrow therapeutic time window
- Early intervention critical for stroke care
- Prehospital personnel

- Telestroke contributes to more efficient use of resources and reduces the time to treatment (AHA/ASA recommendation 2009)

- Intravenous thrombolysis via telestroke consultation of 18% to 36% compared with nationally reported rates of 5% to 8%

Bringing the Hospital to the Patient
- Audebert et al, Berlin

Equipped with a CT scanner, a point-of-care laboratory, and a telemedicine module.
Multimodal Imaging

Curr Neuro and Neuroscience Reports Jan 2010
IV tissue plasminogen activator (tPA)

- Only FDA-approved acute stroke drug
- 3 hour treatment window

IV tpa Extended Window up to 4.5 hours
AHA and ASA endorsed, not FDA approved
Updated Criteria for IV tPA

**Inclusion**
- Measurable neurologic deficit
- Onset < 3 hours
- Age >18

**Relative Exclusion**
- Only minor or rapidly improving symptoms
- Pregnancy
- Seizure at onset
- Major surgery or serious trauma in 14 days
- Recent GI or GU hemorrhage in 21 days
- Recent acute MI within last 3 months

**Exclusion**
- Head trauma or stroke in previous 3 months
- SAH
- Arterial puncture at noncompressible site in previous 7 days
- History of ICH
- Intracranial neoplasm, AVM, aneurysm
- Active Internal Bleeding
- Platelet count <100K
- SBP >185 or DBP >100
- Heparin within 48 hours with elevated PTT
- INR >1.7 or PT>15s
- Direct thrombin or Factor Xa inhibitors
- Blood glucose <50
- CT with hypodensity >1/3 hemisphere
NINDS tPA Stroke Study (Trials)
Part 1 (312) / Part 2 (312): Total 624 Patients
All Under 3 Hrs (Half Under 1.5 Hrs)

NIHSS Excellent Recovery

<table>
<thead>
<tr>
<th></th>
<th>tPA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>20</td>
<td></td>
</tr>
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</table>

p < .05

Total Death

<table>
<thead>
<tr>
<th></th>
<th>tPA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>8</td>
<td>20</td>
</tr>
</tbody>
</table>

Hemorrhage

<p>| | |</p>
<table>
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<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>tPA</td>
<td>9</td>
</tr>
<tr>
<td>Placebo</td>
<td>1</td>
</tr>
</tbody>
</table>
Ischemic Stroke

• For almost two decades, intravenous (IV) recombinant tissue plasminogen activator (rtPA) was the only proven treatment for acute ischemic stroke

  • A key advantage of IV rtPA is that it can be started rapidly after clinical assessment and computed tomography (CT) of the brain without the use of contrast material

  • A disadvantage is its modest rate of effective reperfusion among patients with a large vessel occlusion
Intraarterial t-PA:
Proven, Not FDA Approved

• Similar to cardiac lysis vs. urgent cath
• PROACT I/II studies: pro-urokinase
• Effective up to 6 hours after onset
Endovascular Therapy (EVT)
Proven, FDA Approved
Positive Randomized clinical trials

NEW ENGLAND JOURNAL OF MEDICINE, 2015

**Study Design Factors**

- Documented large vessel occlusion with imaging
- Timely treatment
- New generation devices (primarily stent-retrievers)

Stent Retrievers
Updated AHA Guidelines

Endovascular intervention is now recommended and approved therapy for early management of ischemic stroke

UCLA Health

Endovascular Thrombectomy - Patient Education
## Treatment in the late arriving patients

### 2.2.4. Mechanical Thrombectomy Eligibility—Multimodal Imaging

<table>
<thead>
<tr>
<th>1. When selecting patients with AIS within 6 to 24 hours of last known normal who have LVO in the anterior circulation, obtaining CTP or DW-MRI, with or without MRI perfusion, is recommended to aid in patient selection for mechanical thrombectomy, but only when patients meet other eligibility criteria from one of the RCTs that showed benefit from mechanical thrombectomy in this extended time window.</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>A</td>
</tr>
</tbody>
</table>

### Image Selected Patients

**Occlusion of the ICA and/or MCA M1**

- Both studies randomized patients with large vessel occlusions, small infarcts with salvagable tissue
- **DAWN:** 6-24 HOURS
- **DEFUSE 3:** 6-16 HOURS
Take Home Message IVT

• IV alteplase is the first FDA approved treatment for acute ischemic stroke within 3 hour onset

• 4.5 hour window is not FDA approved but AHA/ASA endorsed as per guidelines

• Earlier administration increases the chance of a good outcome
Take Home Message EVT

• Several positive trials show improved clinical outcomes

• Time matters...get there early

• In select patients, with favorable imaging characteristics the window for treatment may extend up to 24 hours

Minutes Matter

• IV TPA
  » Every 8 minute delay causes 1 fewer of 100 treated patients to benefit in improved ambulation

• IA Neurothrombectomy
  » Every 4 minute delay causes 1 fewer of 100 reperfused patients to benefit in reduced final disability

UCLA Stroke Center
Secondary Prevention

AHA/ASA GUIDELINE

2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack

A Guideline From the American Heart Association/American Stroke Association

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

Endorsed by the Society of Vascular and Interventional Neurology

The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.

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Key Words: AHA Scientific Statements • ischemic attack, transient • secondary prevention • stroke
Algorithm for Evaluating Patient with stroke for optimizing prevention of recurrent ischemic stroke
STROKE RISK REDUCTION STRATEGIES
ATRIAL FIBRILLATION

ACC/AHA/HRS/ESC Recommendations for Stroke Prevention in AF

STROKE RISK

CHADS2-VASc Risk Score

CHADS2-VASc Adjusted Stroke Rate (%/year)

1. Congestive heart failure
2. Hypertension
3. Age ≥75
4. Diabetes
5. Stroke/TIA
6. Thrombocytopenia
7. Vascular disease
8. Age 65-74
9. Female
10. LAA occlusion devices may be considered in patients with clear coexisting risk factors for CAC (1bC)

Steffen J et al. EHRA Practical Guide to NOACs EHU 2018


Letter Clinical characteristic Points awarded

H Hypertension 1
A Abnormal renal function (1 point each) 1 or 2
S Stroke 1
B Bleeding 1
L Labile INR 1
E Elderly (≥ age 75 years) 1
D Drugs or alcohol (1 point each) 1 or 2
High Risk: score ≥ 3 Maximum 9 points

Anticoagulation for AF is a core measure - wait new document (a reason for not prescribing)
Major DOAC Clinical Trials

- **RELY Trial** - NEJM Sept 17th, 2009  
  - Dabigatran versus Warfarin in Patients with Atrial Fibrillation (n=18,113)

- **ROCKET AF Trial** - NEJM August 8th, 2011  
  - Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation (n=14,266)

- **ARISTOTLE Trial** - NEJM September 15th, 2011  
  - Apixaban versus Warfarin in Patients with Atrial fibrillation (n=18,206)

- **ENGAGE AF Trial** - NEJM Nov 28th, 2013  
  - Edoxaban versus Warfarin in Patients with Atrial Fibrillation (n=21,105)

- **PREVAIL Trial** - JACC July 8th, 2014  
  - Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure Device in patients with atrial fibrillation versus long term warfarin (n=269 – Watchman, n=138 – Warfarin; total=437)

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Comparative Stroke, Bleeding, and Mortality Risks in Older Medicare Patients Treated with Oral Anticoagulants for Nonvalvular Atrial Fibrillation.

![Graph showing comparative risks](image)

- n=183,318 Medicare patients, followed 2010-2015
- Mean age 75.2 years (71-73 in the MAJOR TRIALS)

But my patient is a fall risk......

- **Anticoagulate anyway!**

  - “Fall risk” – need to fall **295** times per year to not benefit from warfarin

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Man-son-Hing et al. Choosing Antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. Arch Int Med 159, April 1999
### Antithrombotic Agents

#### Table: Characteristics of Key Antithrombotic Trials and Meta-Analyses in Stroke/TIA

<table>
<thead>
<tr>
<th>Trial or Meta-Analysis</th>
<th>Patient Population</th>
<th>Antithrombotic Intervention</th>
<th>Follow-Up (mo)</th>
<th>Key Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspire</td>
<td>19,301 patients with acute ischemic stroke within 48 h of symptom onset</td>
<td>Aspirin 300 mg vs placebo</td>
<td>6</td>
<td>6.8 fewer cases of death or non-fatal stroke per 1000 treated at 6 mo</td>
</tr>
<tr>
<td>CAST</td>
<td>71,167 patients with acute ischemic stroke within 48 h of symptom onset</td>
<td>Aspirin 100 mg vs placebo</td>
<td>4</td>
<td>6.8 fewer cases of death or non-fatal stroke per 1000 treated at 4 wk</td>
</tr>
<tr>
<td>6E + CASI®-based studies</td>
<td>40,617 patients with acute ischemic stroke within 48 h of symptom onset</td>
<td>Aspirin 100-325 mg vs no aspirin</td>
<td>2</td>
<td>6.1 fewer cases of stroke or death in hospital per 1000 treated</td>
</tr>
<tr>
<td>AND 2 meta-analyses</td>
<td>07/10 secondary prevention patients in 10 placebo/TIA aspirin trials</td>
<td>Aspirin (variable dose)</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>ASA-studies</td>
<td>20,002 patients with a completed ischemic stroke or TIA within the past 3 mo</td>
<td>Aspirin 30 mg bid, dipiridamole 200 mg bid, aspirin 30 mg bid + dipyridamole 200 mg bid, or placebo</td>
<td>2 y</td>
<td>Composite stroke or death was reduced by 15.8% (P=0.019) with aspirin + dipyridamole and by 14.4% (P=0.057) with aspirin/dipyridamole</td>
</tr>
<tr>
<td>ESPRIT</td>
<td>27,341 patients within 6 mo of a TIA or minor ischemic stroke of presumed arterial origin</td>
<td>Aspirin 70-350 mg daily and dipyridamole 200 mg BID vs aspirin 30-125 mg daily alone</td>
<td>3.5 y</td>
<td>Composite of death from all causes, non-fatal stroke, non-fatal myocardial infarction, or major bleeding complications was reduced by aspirin+dipyridamole (HR: 0.80, 95% CI: 0.65-0.96), no increase in major bleeding complications (HR: 0.67, 95% CI: 0.44-1.09)</td>
</tr>
</tbody>
</table>

**Meta-analyses**

**CAPRIE**

16,165 patients with recent ischemic stroke, recent MI, or peripheral arterial disease, or included in 784 with recent ischemic stroke |

**MATCH**

18,683 patients with recent ischemic stroke or TIA and at least 1 additional vascular risk factor |

**SPS3**

30,203 patients with symptomatic carotid stenosis in the preceding 180 days |

**CHARISMA**

10,674 patients with cardiovascular disease or multiple risk factors, included n=600 with prior ischemic stroke |

**PROGRESS**

20,223 patients with a recent ischemic stroke (HR=2.26) |

**CHARACTER**

6172 patients within 24 h after the onset of minor ischemic stroke or TIA and at least 1 additional vascular risk factor |

**POINT**

46,811 patients within 12 h after the onset of minor ischemic stroke or TIA |

**GORGEOUS**

15,165 patients with nonvalvular ischemic stroke or high-risk TIA within 24 h |

**ATPRO meta-analysis**

86,100 patients with acute ischemic stroke, recent MI, or peripheral arterial disease |
CHANCE Trial

Randomly assigned to clopidogrel aspirin (loaded with 300mg clopidogrel and then 75mg up to day 90)

NNT = 29 to prevent one stroke over 90 days
Point trial

BACKGROUND
Combination antiplatelet therapy with clopidogrel and aspirin may reduce the rate of recurrent stroke during the first 3 months after a minor ischemic stroke or transient ischemic attack (TIA). A trial of combination antiplatelet therapy in a Chinese population has shown a reduction in the risk of recurrent stroke. We tested this combination in an international population.

METHODS
In a randomized trial, we assigned patients with minor ischemic stroke or high-risk TIA to receive either clopidogrel at a loading dose of 600 mg on day 1, followed by 75 mg per day, plus aspirin (at a dose of 30 to 325 mg per day) or the same range of doses of aspirin alone. The dose of aspirin in each group was selected by the site investigator. The primary efficacy outcome in a time-to-event analysis was the risk of a composite of major ischemic events, which was defined as ischemic stroke, myocardial infarction, or death from an ischemic vascular event, at 90 days.

RESULTS
A total of 4881 patients were enrolled at 269 international sites. The trial was halted after 84% of the anticipated number of patients had been enrolled because the data and safety monitoring board had determined that the combination of clopidogrel and aspirin was associated with both a lower risk of major ischemic events and a higher risk of major hemorrhage than aspirin alone at 90 days. Major ischemic events occurred in 121 of 2432 patients (5.0%) receiving clopidogrel plus aspirin and in 160 of 2449 patients (6.5%) receiving aspirin plus placebo (hazard ratio, 0.75; 95% confidence interval [CI], 0.59 to 0.95; P=0.02), with most events occurring during the first week after the initial event. Major hemorrhage occurred in 23 patients (0.9%) receiving clopidogrel plus aspirin and in 10 patients (0.4%) receiving aspirin plus placebo (hazard ratio, 2.32; 95% CI, 1.10 to 4.87; P=0.02).

CONCLUSIONS
In patients with minor ischemic stroke or high-risk TIA, those who received a combination of clopidogrel and aspirin had a lower risk of major ischemic events but a higher risk of major hemorrhage at 90 days than those who received aspirin alone. (Funded by the National Institute of Neurological Disorders and Stroke; POINT ClinicalTrials.gov number, NCT00991029.)

for every 1000 patients treated, prevent 15 strokes, cause 5 hemorrhages
THALES Trial

- Reversible P2Y_{12} receptor antagonist, which unlike clopidogrel, does not require conversion from prodrug to active drug in the liver

CONCLUSIONS
Among patients with a mild-to-moderate acute noncardioembolic ischemic stroke (NIHSS score ≤5) or TIA who were not undergoing intravenous or endovascular thrombolysis, the risk of the composite of stroke or death within 30 days was lower with ticagrelor–aspirin than with aspirin alone, but the incidence of disability did not differ significantly between the two groups. Severe bleeding was more frequent with ticagrelor. (Funded by AstraZeneca; THALES ClinicalTrial.gov number, NCT03354429.)

Ticagrelor is reversible and short acting, so must be given twice daily.
Antiplatelet Algorithm

Dual Antiplatelet Therapy Versus Aspirin in Minor Stroke or TIA

Meta-Analysis of Randomized Controlled Trials

4 trials, 21,459 patients with minor stroke or high-risk TIA

<table>
<thead>
<tr>
<th></th>
<th>Aspirin + P2Y12i</th>
<th>Aspirin + Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>10,737</td>
<td>10,722</td>
</tr>
<tr>
<td>Recurrent Stroke (N)</td>
<td>626</td>
<td>827</td>
</tr>
<tr>
<td>RR</td>
<td>0.76; 95% CI, 0.68-0.83; P&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Major Bleed (N)</td>
<td>71</td>
<td>29</td>
</tr>
<tr>
<td>RR</td>
<td>2.2; 95% CI, 1.14-4.34; P=0.02</td>
<td></td>
</tr>
</tbody>
</table>

In minor stroke or high-risk TIA, short term DAPT reduced the risk of recurrent stroke at the expense of a higher risk of major bleeds

Kirtipla Bhatia. Stroke. Dual Antiplatelet Therapy Versus Aspirin in Patients With Stroke or Transient Ischemic Attack: Meta-Analysis of Randomized Controlled Trials, Volume: 52, Issue: 6, Pages: e217-e223, DOI: (10.1161/STROKEAHA.120.030333)
## Recommendations for Hypertension

Referenced studies that support recommendations are summarized in online Data Supplements 11 and 12.

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>1. In patients with hypertension who experience a stroke or TIA, treatment with a thiazide diuretic, angiotensin-converting enzyme inhibitor, or angiotensin II receptor blockers is useful for lowering BP and reducing recurrent stroke risk.(^{185-189})</td>
</tr>
<tr>
<td>1</td>
<td>B-R</td>
<td>2. In patients with hypertension who experience a stroke or TIA, an office BP goal of &lt;130/80 mmHg is recommended for most patients to reduce the risk of recurrent stroke and vascular events.(^{185,190-194})</td>
</tr>
<tr>
<td>1</td>
<td>B-NR</td>
<td>3. In patients with hypertension who experience a stroke or TIA, individualized drug regimens that take into account patient comorbidities, agent pharmacological class, and patient preference are recommended to maximize drug efficacy.(^{188,189,195,196})</td>
</tr>
<tr>
<td>2a</td>
<td>B-R</td>
<td>4. In patients with no history of hypertension who experience a stroke or TIA and have an average office BP of (\geq 130/80) mmHg, antihypertensive medication treatment can be beneficial to reduce the risk of recurrent stroke, ICH, and other vascular events.(^{190,191,193,197})</td>
</tr>
</tbody>
</table>
Diabetes mellitus

### Recommendations for Glucose

Referenced studies that support recommendations are summarized in online Data Supplements 14 and 15.

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>1. In patients with an ischemic stroke or TIA who also have diabetes, the goal for glycemic control should be individualized based on the risk for adverse events, patient characteristics and preferences, and, for most patients, especially those &lt;65 years of age and without life-limiting comorbid illness, achieving a goal of HbA1c ≤7% is recommended to reduce risk for microvascular complications.</td>
</tr>
<tr>
<td>1</td>
<td>B-R</td>
<td>2. In patients with an ischemic stroke or TIA who also have diabetes, treatment of diabetes should include glucose-lowering agents with proven cardiovascular benefit to reduce the risk for future major adverse cardiovascular events (ie, stroke, MI, cardiovascular death).</td>
</tr>
<tr>
<td>1</td>
<td>C-EO</td>
<td>3. In patients with an ischemic stroke or TIA who also have diabetes, multidimensional care (ie, lifestyle counseling, medical nutritional therapy, diabetes self-management education, support, and medication) is indicated to achieve glycemic goals and to improve stroke risk factors.</td>
</tr>
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### Lipids

#### Recommendations for Treating and Monitoring Hyperlipidemia

Referenced studies that support recommendations are summarized in online Data Supplement 12.

<table>
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<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td>1</td>
<td>A</td>
<td>1. In patients with ischemic stroke with no known coronary heart disease, no major cardiac sources of embolism, and LDL cholesterol (LDL-C) &gt;100 mg/dL, atorvastatin 80 mg daily is indicated to reduce risk of stroke recurrence.(^{208,209})</td>
</tr>
<tr>
<td>1</td>
<td>A</td>
<td>2. In patients with ischemic stroke or TIA and atherosclerotic disease (intracranial, carotid, aortic, or coronary), lipid-lowering therapy with a statin and also ezetimibe, if needed, to a goal LDL-C of &lt;70 mg/dL is recommended to reduce the risk of major cardiovascular events.(^{210})</td>
</tr>
<tr>
<td>2a</td>
<td>B-NR</td>
<td>3. In patients with ischemic stroke who are very high risk (defined as stroke plus another major ASCVD or stroke plus multiple high-risk conditions), are taking maximally tolerated statin and ezetimibe therapy and still have an LDL-C &gt;70 mg/dL, it is reasonable to treat with PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor therapy to prevent ASCVD events.(^{211-213})</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Monitoring</strong></td>
</tr>
<tr>
<td>1</td>
<td>A</td>
<td>4. In patients with stroke or TIA and hyperlipidemia, patients’ adherence to changes in lifestyle and the effects of LDL-C-lowering medication should be assessed by measurement of fasting lipids and appropriate safety indicators 4 to 12 weeks after statin initiation or dose adjustment and every 3 to 12 months thereafter, based on need to assess adherence or safety.(^{214,215})</td>
</tr>
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## Carotid Disease

### Recommendations for Extracranial Carotid Stenosis

**Recommended studies that support recommendations are summarized in online Data Supplement 3.**

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>1. In patients with a TIA or non-disabling ischemic stroke within the past 6 months and ipsilateral severe (70%-99%) carotid artery stenosis, carotid endarterectomy (CEA) is recommended to reduce the risk of future stroke, provided that perioperative morbidity and mortality risk is estimated to be &lt;6%.208</td>
</tr>
<tr>
<td>1</td>
<td>A</td>
<td>2. In patients with ischemic stroke or TIA and symptomatic extracranial carotid stenosis who are scheduled for carotid artery stenting (CAS) or CEA, procedures should be performed by operators with established periprocedural stroke and mortality rates of &lt;6% to reduce the risk of surgical adverse events.207</td>
</tr>
<tr>
<td>1</td>
<td>A</td>
<td>3. In patients with carotid artery stenosis and a TIA or stroke, intensive medical therapy, with antiplatelet therapy, lipid-lowering therapy, and treatment of hypertension, is recommended to reduce stroke risk.203</td>
</tr>
<tr>
<td>1</td>
<td>B-R</td>
<td>4. In patients with recent TIA or ischemic stroke and ipsilateral moderate (60%-69%) carotid stenosis as documented by catheter-based imaging or noninvasive imaging, CEA is recommended to reduce the risk of future stroke, depending on patient-specific factors such as age, sex, and comorbidities, if the perioperative morbidity and mortality risk is estimated to be &lt;6%.208</td>
</tr>
<tr>
<td>2a</td>
<td>B-R</td>
<td>5. In patients ≥70 years of age with stroke or TIA in whom carotid revascularization is being considered, it is reasonable to select CEA over CAS to reduce the periprocedural stroke rate.271</td>
</tr>
<tr>
<td>2a</td>
<td>B-R</td>
<td>6. In patients in whom revascularization is planned within 1 week of the index stroke, it is reasonable to choose CEA over CAS to reduce the periprocedural stroke rate.272</td>
</tr>
</tbody>
</table>

### Recommendations for Extracranial Carotid Stenosis (Continued)

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>C-LD</td>
<td>7. In patients with TIA or nondisabling stroke, when revascularization is indicated, it is reasonable to perform the procedure within 2 weeks of the index event rather than delay surgery to increase the likelihood of stroke-free outcome.273</td>
</tr>
<tr>
<td>2a</td>
<td>C-LD</td>
<td>8. In patients with symptomatic severe stenosis (≥70%) in whom anatomic or medical conditions are present that increase the risk for surgery (such as radiation-induced stenosis or restenosis after CEA) it is reasonable to choose CAS to reduce the periprocedural complication rate.204</td>
</tr>
<tr>
<td>2b</td>
<td>A</td>
<td>9. In symptomatic patients at average or low risk of complications associated with endovascular intervention, when the ICA stenosis is ≥70% by noninvasive imaging or ≥60% by catheter-based imaging and the anticipated rate of periprocedural stroke or death is &lt;8%, CAS may be considered as an alternative to CEA for stroke prevention, particularly in patients with significant cardiovascular comorbidities predisposing to cardiovascular complications with endarterectomy.205</td>
</tr>
<tr>
<td>2b</td>
<td>B-NR</td>
<td>10. In patients with a recent stroke or TIA (past 6 months), the usefulness of transcatheter artery revascularization (TCHAR) for prevention of recurrent stroke and TIA is uncertain.206</td>
</tr>
<tr>
<td>3</td>
<td>No Benefit</td>
<td>11. In patients with recent TIA or ischemic stroke and when the degree of stenosis is &lt;50%, revascularization with CEA or CAS to reduce the risk of future stroke is not recommended.209</td>
</tr>
<tr>
<td>3</td>
<td>No Benefit</td>
<td>12. In patients with a recent (within 120 days) TIA or ischemic stroke ipsilateral to atherosclerotic stenosis or occlusion of the middle cerebral or carotid artery, extracranial-intracranial bypass surgery is not recommended.207</td>
</tr>
</tbody>
</table>
It is now considered reasonable to percutaneously close PFO in patients who meet each of the following criteria: age 18–60 years, non-lacunar stroke, no other identified cause, and high risk patent foramen ovale features.
Take home: Patients assigned to an energy-unrestricted Mediterranean diet, supplemented with extra-virgin olive oil or nuts, had a lower rate of major cardiovascular events than those assigned to a reduced-fat diet.
EXERCISE

Exercise

• 2003 Meta-Analysis 23 cohort and case-control studies
  • 27% relative risk reduction stroke and mortality with physical activity

Healthy Lifestyle

• 2008 Prospective Cohort Study N= 114,928
  • 80% (women), 70% (men) risk reduction in stroke
  • Up to 54% of strokes may be prevented by healthy lifestyle

Cost: NONE! FREE!!

Lee 2003, Chiuve 2008
Depression

- Underdiagnosed – seen in 1/3 stroke patients
- Pathophysiology poorly understood
- Natural history dynamic but typically will develop in the 1st year
- Undertreated – associated with higher mortality and poor functional recovery
- FLAME trial: ?improved motor recovery in fluoxetine group, small study; EFFECTS, AFFINITY, FOCUS: larger studies, no benefit on functional outcome of fluoxetine versus placebo at 6 month
- Screen your patients
- Antidepressant may be useful and effective but unclear as to optimal timing, medication, can consider neuromodulation, psychosocial interventions, but no RCT, placebo controlled trials
Take Home Message: Secondary Prevention

- TIA’s: VIP target risk reduction
- Atrial fibrillation **LOOK FOR IT**
  - Anticoagulation
- Non-cardioembolic stroke or TIA
  - Antiplatelet therapies
- Underlying risk factor management
  - HTN, DM, Cholesterol, Tobacco, Exercise, Diet, Screen for depression
- Carotid stenosis
  - Carotid endarterectomy / Carotid Stenting
- PFO Treatment
  - Tailor to the patient, closure versus medical management in select patients, decision made in conjunction with neurology