Recurrent Stroke Prevention:  
An Update on the  
Evidence and Opportunity in  
Ischemic Stroke or TIA  

Case-Based Review of Guidelines for Practitioners Who Care for Patients With Ischemic Stroke or TIA

Impact of Stroke in the United States

- Of all CVDs, stroke is the third leading cause of death
- Annual incidence
  - 780,000 strokes
  - 600,000 first attacks
  - 180,000 recurrent attacks
- 15% of strokes are heralded by TIA
- One-third of TIAs may be considered cerebral infarctions based on diffusion-weighted MRI results
- 90-day risk of stroke after TIA: 3%–17%
  - Highest risk within the first 30 days

CVD = cardiovascular disease; MRI = magnetic resonance imaging

Estimates of the Cost of Stroke

Average cost of ischemic stroke within 30 days  
- $13,019 (mild)  
- $20,346 (severe)

Mean lifetime cost of ischemic stroke  
- $160,048

$65.5 billion* in 2008

*Estimated direct and indirect costs

American Heart Association, Heart Disease and Stroke Statistics–2008 Update.
Dallas, Texas: American Heart Association; 2008;
Rosamond W et al. Circulation. 2008;117(4);e25

Estimates of Long-term Risk of Stroke After Ischemic Stroke or TIA

Percentage of Patients Experiencing Stroke

<table>
<thead>
<tr>
<th>Time</th>
<th>After TIA1 (%)</th>
<th>After Stroke2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 days</td>
<td>4–8</td>
<td>3–10</td>
</tr>
<tr>
<td>1 year</td>
<td>12–13</td>
<td>10–14</td>
</tr>
<tr>
<td>5 years</td>
<td>24–29</td>
<td>25–40</td>
</tr>
</tbody>
</table>


Putative Risk Factors for Stroke Recurrence

Early stroke recurrence
- Stroke subtype
  - High for large artery, extra- and intracranial occlusive disease
- Elevated blood glucose
- HTN

Late stroke recurrence
- Age
- HTN
- Heart disease (CHD, HF, AF)
- DM and hyperglycemia

Prior stroke or TIA

AF = atrial fibrillation; CHD = coronary heart disease; DM = diabetes mellitus; HF = heart failure; HTN = hypertension


Defining Stroke Subtype Is an Important Consideration in Recurrent Stroke Prevention

- Hemorrhagic stroke 12%
- Cryptogenic 5%
- Atherosclerotic cerebrovascular disease 25%
- Small vessel disease "lacunes" 25%
- Ischemic stroke 88%

Albers GW et al. Chest. 2004;126(3 suppl):438S
Thom T et al. Circulation. 2006;113(6);e85
Prevention of Recurrent Stroke

- Evaluation for risk factors
  - HTN, DM, hyperlipidemia
- Evaluation for cause
  - Arterial diseases, heart diseases
  - Coagulopathies
- Management of risk factors
  - Lifestyle and medications
- Antithrombotic therapy
- Surgical or endovascular interventions

Sacco RL et al. Stroke. 2006;37(2):577

Case Presentation

65-Year-Old Woman With 15-Year History of HTN

- Chief complaint
  - Presented to the ED after a 30-minute spell of transient right-sided face and arm weakness after exercising today
- Past medical history
  - HTN × 15 years
- Medications
  - HCTZ 25 mg once daily

ED = emergency department; HCTZ = hydrochlorothiazide

65-Year-Old Woman With 15-Year History of HTN

- Physical exam
  - BP 149/95 mm Hg; HR 80 BPM and regular
  - Neurologic examination normal except for slight weakness of the right arm and leg (NIH Stroke Scale score = 2)
- Laboratory examination
  - Total cholesterol = 230 mg/dL
  - LDL-C = 120 mg/dL
  - HDL-C = 39 mg/dL
  - Other laboratory tests unremarkable

BP = blood pressure; ED = emergency department; HDL-C = high-density lipoprotein cholesterol; HR = heart rate; LDL-C = low-density lipoprotein cholesterol; NIH = National Institutes of Health

65-Year-Old Woman With 15-Year History of HTN

- Diagnostic studies
  - EKG normal
  - Transthoracic echocardiography showed LVH
  - MRA of the head and neck was unremarkable
  - MRI of the head

EKG = electrocardiogram
LVH = left ventricular hypertrophy
MRA = magnetic resonance angiography

MRI Diffusion-Weighted Imaging (DWI)

MRI Diffusion-Weighted Imaging (DWI)

[Image of MRI Diffusion-Weighted Imaging]
65-Year-Old Woman With 15-Year History of HTN

- Diagnostic studies
  - EKG is normal
  - Transthoracic echocardiography showed LVH
  - MRA of the head and neck was unremarkable
  - MRI of head shows DWI abnormality predominantly of left posterior limb of internal capsule consistent with ischemic injury

Guidelines for Management of TIA

Definitions of Classes and Levels of Evidence: AHA/ASA 2006 Stroke Prevention Guidelines

<table>
<thead>
<tr>
<th>Class</th>
<th>Evidence or general agreement that procedure or treatment is useful and effective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Conflicting evidence or divergence of opinion of usefulness/efficacy</td>
</tr>
<tr>
<td>Class II</td>
<td>Weight of evidence or opinion is in favor</td>
</tr>
<tr>
<td>Class IIa</td>
<td>Usefulness/efficacy is less well established by evidence or opinion</td>
</tr>
<tr>
<td>Class IIb</td>
<td>Evidence and general opinion that usefulness/effectiveness does not exist and may be harmful</td>
</tr>
<tr>
<td>LOE A</td>
<td>Derived from multiple RCTs</td>
</tr>
<tr>
<td>LOE B</td>
<td>Derived from a single RCT or nonrandomized studies</td>
</tr>
<tr>
<td>LOE C</td>
<td>Expert opinion or case series</td>
</tr>
</tbody>
</table>

Recent TIA: A Neurologic Emergency

- Risk of stroke after TIA
  - 10.5% occurred within 90 days and half occurred within 2 days (Kaiser-Permanente HMO study)
- Risks may have been previously underestimated
  - 1%–2% at 7 days and 2%–4% at 30 days
- True risk
  - Up to 10% at 7 days and as high as 15% at 30 days
- Time window for prevention is brief
  - 17% of TIA occur on the day of stroke
  - 43% during the 7 days prior to stroke

Predicting Risk of Stroke After TIA: ABCD² Score for 2- or 7-Day Risk of Stroke

| A | Age ≥60 years | 1 point |
| B | Blood pressure SBP >140 mm Hg or DBP >90 mm Hg | 1 point |
| C | Clinical features
  - Unilateral weakness | 2 points |
  - Speech disturbance without weakness | 1 point |
| D | Duration of symptoms
  - 240 minutes | 2 points |
  - 10-59 minutes | 1 point |
| D | Diabetes | 1 point |

Maximum score 7 points

DBP = diastolic blood pressure; SBP = systolic blood pressure

Johnston SC et al. Lancet. 2007;369(9558):283
**ABCD² Score Level of Risk 2-Day Stroke Risk (%)**

<table>
<thead>
<tr>
<th>ABCD² Score</th>
<th>Level of Risk</th>
<th>2-Day Stroke Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6–7</td>
<td>High</td>
<td>8.1</td>
</tr>
<tr>
<td>4–5</td>
<td>Moderate</td>
<td>4.1</td>
</tr>
<tr>
<td>0–3</td>
<td>Low</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*Johnston SC et al. Lancet. 2007;369(9553):283*

**Traditional TIA Symptoms and Signs**: Carotid Territory (1974)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Sign</th>
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</thead>
<tbody>
<tr>
<td>1. Motor dysfunction</td>
<td>Weakness, clumsiness, paralysis of 1 or both limbs on same side</td>
</tr>
<tr>
<td>2. Sensory</td>
<td>Numbness, loss of sensation, and paresthesias of 1 or both limbs on same side without spread or march</td>
</tr>
<tr>
<td>3. Speech/language</td>
<td>Aphasia</td>
</tr>
<tr>
<td>4. Vision</td>
<td>Loss in 1 eye or part of 1 eye</td>
</tr>
<tr>
<td>5. Vision</td>
<td>Homonymous hemianopia</td>
</tr>
<tr>
<td>6. Multiple</td>
<td>Combination of above</td>
</tr>
</tbody>
</table>

*Symptoms/sign can last up to 24 hours

*Heyman A et al. Stroke 1974;9:277*


**Definition**
- Brief episode of neurologic dysfunction caused by focal brain or retinal ischemia
- Clinical symptoms typically lasting less than 1 hour
- No evidence of cerebral infarction (using advanced neuroimaging techniques)
- Urgent brain imaging is recommended

**Rationale**
- Traditional definition is out of date and no longer consistent with current concepts of brain ischemia
- Most TIs are short lived, and advanced imaging techniques may show cerebral ischemic injury

*Heyman A et al. Stroke 1974;9:277

**National Stroke Association (NSA) Guidelines for the Management of TIAs**

**Factor**
**Comment**

<table>
<thead>
<tr>
<th>Hospitalization</th>
<th>• Consider within 24–48 hours of first TIA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Timely hospital referral of recent (within 1 week) TIA and hospital admission is generally recommended in the case of crescendo TIAs. Symptoms longer than 1 hour, associated with headache, syncope, vertigo, tinnitus, unsteady gait, or visual difficulties.</td>
</tr>
<tr>
<td></td>
<td>• Hospital admission should be immediate even if patient is hemodynamically stable or asymptomatic during hospital evaluation.</td>
</tr>
<tr>
<td></td>
<td>• Urgent brain imaging is recommended.</td>
</tr>
<tr>
<td></td>
<td>• Hospitals/practitioners should have local admission policy and referral policy for specialists’ assessment.</td>
</tr>
<tr>
<td></td>
<td>• Local written protocols for diagnostic testing.</td>
</tr>
</tbody>
</table>

**Clinical evaluation**
- Specialized clinic for rapid assessment and evaluation within 24–48 hours

**Timing of initial assessment**
- For recent TIA, need same-day access to imaging such as CT/CTA, MRA, and/or CUS
- If not admitted to hospital, rapid (within 12 hours) access to urgent assessment and investigation
- If TIA occurred in past 2 weeks and patient was not hospitalized, prompt (24–48 hour) investigations (CUS, blood work, EKG, echocardiogram) needed

*Heyman A et al. Stroke 1974;9:277

**NSA Guidelines for the Management of TIAs: Evaluation**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>EKG, CBC, serum electrolytes, creatinine, fasting blood glucose, lipids</td>
</tr>
<tr>
<td>Brain imaging</td>
<td>CT/CTA or MRI/CT, TCD is complementary</td>
</tr>
<tr>
<td>Carotid imaging</td>
<td>Doppler ultrasound; CTA and/or MRA for supra-aortic vessels if Doppler not reliable or CEA considered; conventional angiogram if Doppler and MRA/CTA discordant or not feasible</td>
</tr>
<tr>
<td>Cardiac evaluation</td>
<td>TTE or TEE in patients younger than 45 years when neck, brain, and hematologic studies negative for cause</td>
</tr>
</tbody>
</table>

*CBC = complete blood count |
*CEA = carotid endarterectomy |
*TCD = transcranial Doppler |
*TEE = transesophageal echocardiogram |
*TTE = transthoracic echocardiogram |

*Heyman A et al. Stroke 1974;9:277

**Medical and Surgical Management of TIAs**

- NSA and AHA/ASA guidelines for use of antithrombotic therapies, CEA, EC-IC bypass, and medical risk-factor modification for TIA patients are comparable
- These prevention strategies in TIA and ischemic stroke patients plus angioplasty and stenting are reviewed in subsequent sections of this activity according to 2006 and 2008 AHA/ASA guidelines

*Heyman A et al. Stroke 1974;9:277

**EC-IC = extracranial-intracranial**

*Heyman A et al. Stroke 1974;9:277

*Adams RJ et al. Stroke 2008;39(5):1647*
Does Rapid Assessment and Treatment of TIA/Minor Stroke Lead to Improved Outcomes? EXPRESS Study

- Urgent assessment and immediate clinical treatment in Oxford Vascular Study (OXVASC) of those at risk of stroke within 90 days
- Phase 1 (4/1/02–9/30/04); Phase 2 (10/1/04–3/31/07)

![Graph](image)

Pr.0001 2.1

Early treatment associated with 80% reduction

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65-Year-Old Woman With 15-Year History of HTN

- Case impression
  - No evidence of cardiac source of embolism or high-grade carotid stenosis

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AHA/ASA 2008 Recurrent Stroke Prevention Guideline Update

- Acceptable antiplatelet options for initial recurrent stroke prevention (Class I, LOE A)
  - ASA (50–325 mg/day)
  - ASA plus ER dipyridamole (25 mg/200 mg bid)
  - Clopidogrel (75 mg/day)

- Other recommendations
  - ASA plus ER dipyridamole favored over ASA alone (Class 1, LOE B; upgraded based on ESPRIT study result)*
  - ASA added to clopidogrel is not recommended for routine use

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Guidelines for Use of Antiplatelet Therapy in TIA or Ischemic Stroke Prevention

- Resting platelet
- Activated platelets
  - (Scanning electron microscopy)

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Which one of the following antiplatelet agents are acceptable for prevention of recurrent cerebral ischemia according to current guidelines?

A. Aspirin
B. Aspirin plus extended-release dipyridamole
C. Clopidogrel
D. Aspirin, aspirin plus extended-release dipyridamole, or clopidogrel

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“Variable Response” Preferred Term to “Aspirin Resistance”?

- Variable response
  - Occurrence of breakthrough atherothrombotic events
  - Response to ASA differs among patients and may be attributed to various mechanisms

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*New recommendation since 2006 guideline
ASA = aspirin; bid = twice a day; ER = extended release; ESPRIT = European/Australasian Stroke Prevention in Reversible Ischemia Trial

PRoFESS Trial

- Primary end point
  - Across an average observation time of 2.5 years, rates of first recurrent stroke were similar (9.0% ASA + ER dipyridamole vs 8.8% clopidogrel; HR 1.01, 95% CI 0.92–1.11)

- Bleeding
  - More frequent in ASA + ER dipyridamole group (major hemorrhagic events: 4.1% vs 3.6%; HR 1.15, 95% CI 1.00–1.32, P=0.06)

- Benefit-risk ratio
  - Similar between groups (11.7%ASA + ER dipyridamole vs 11.4% clopidogrel; HR 1.03, 95% CI 0.98–1.11, P=0.50)

CI = confidence interval; HR = hazard ratio

Guidelines for Medical Risk Factor Management in Patients With TIA or Ischemic Stroke

65-Year-Old Woman With 15-Year History of HTN

- Diagnosis
  - Patient was diagnosed with a lacunar or small artery territory infarction syndrome

- Treatment
  - She did not receive intravenous tPA therapy since she had only a very minor neurologic impairment
  - After the MRI head study was reviewed in the ED, she was treated with ASA 81 mg/day
  - Her BP was initially not treated

- Within 48 hours of the neurologic symptoms, her neurologic examination was normal

tPA = tissue plasminogen activator

When it is deemed safe to lower BP following the initial phase of acute ischemic stroke, what is the long-term target BP?

A. <140/90 mm Hg
B. <130/80 mm Hg
C. <120/70 mm Hg
D. <110/75 mm Hg
Which one of the following statements best characterizes the use of statin therapy for recurrent stroke prevention?

A. There is no proof that statin therapy reduces stroke risk
B. Statin therapy reduces stroke risk, but is not safe; fatal liver disease is common
C. Statin therapy reduces stroke and major cardiovascular risks
D. Statin therapy reduces stroke risk, but does not reduce major cardiovascular risks

Which one of the following statements best characterizes smoking as a risk factor for stroke?

A. Environmental (passive) smoke increases the risk of stroke
B. Smoking is a risk factor for ischemic, but not hemorrhagic stroke
C. Smoking increases the relative risk of stroke by 5 to 10 times
D. Smoking cessation leads to reversal of stroke risk after 20 years

AHA/ASA 2008 Recurrent Stroke Prevention Guideline Update

- Statin therapy and lipid lowering
  - Based on the SPCRL results, statin therapy with intensive lipid-lowering effects is indicated for patients with LDL-C in the 100–190 mg/dL range, atherosclerotic ischemic stroke or TIA, and no known CHD to reduce occurrence of stroke and vascular events (Class I, LOE B∗)
  - Target goal for cholesterol lowering for those with CHD or symptomatic atherosclerotic disease
    - LDL-C level of <100 mg/dL,
    - LDL-C <70 mg/dL for very high-risk persons (those with multiple risk factors)

*New recommendation since 2006 guideline

AHA/ASA 2006 Recommendations for Lifestyle and Risk Factor Management in TIA or Ischemic Stroke

<table>
<thead>
<tr>
<th>Factor</th>
<th>Recommendation</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN</td>
<td>Initiate Rx when safe; individualize Rx; consider BP reduction of 10/5 mm Hg with a diuretic and ACEI</td>
<td>Class I, LOE A</td>
</tr>
<tr>
<td>DM</td>
<td>Rigorous control of BP and lipids; aim for hemoglobin A1C &lt;6%</td>
<td>Class I, LOE A</td>
</tr>
<tr>
<td>Smoking</td>
<td>Smoking cessation. Counseling, NRT, and oral smoking-cessation medications</td>
<td>Class I, LOE C</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Eliminate heavy drinking or reduce</td>
<td>Class I, LOE A</td>
</tr>
<tr>
<td>Physical activity</td>
<td>If capable, at least 30 minutes of moderate-intensity exercise daily</td>
<td>Class I, LOE A</td>
</tr>
</tbody>
</table>

ACEI = angiotensin-converting enzyme inhibitor; BMI = body mass index; NRT = nicotine replacement therapy; Rx = treatment

Established Therapies Are Consistently Underused in all Patient Types

![Graph showing underuse of therapies](image)
65-Year-Old Woman With 15-Year History of HTN

- Patient is now taking a diuretic, ACEI, statin, and ASA plus ER dipyridamole for recurrent stroke prevention

*What steps might be taken to assure adherence to the treatment regimen?*

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Steps to Consider to Enhance Adherence to TIA or Recurrent Stroke Prevention Regimen

- Awareness or recognition of stroke risk and risk factors
- Qualitative determination of recurrent stroke risk
- Awareness of risk factor numbers (e.g., BP, blood glucose, serum cholesterol)
- Establish multimodality maintenance approach

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Recurrent Stroke Prevention Successful Maintenance of Treatment by Multimodality Approach

- Motivation from family members
- Reminders and encouragement from medical office staff
- Pharmacy reminders to renew medications
- Physician report cards: Is the patient meeting target numbers?

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What Can Stroke Teams Do?

- In-hospital initiation of secondary prevention therapies to increase treatment utilization and adherence in the long term
- Adopt a systematic management approach in coordination with primary care physicians to help optimize post-stroke care

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Cardioembolic Stroke Management

- On physical examination, the patient's pulse is noted to be irregularly irregular. A bedside EKG is ordered

- Patient is diagnosed with cardioembolic stroke secondary to AF
Which one of the following therapies is recommended to prevent stroke recurrence for a high-risk patient with atrial fibrillation?

A. Aspirin
B. Clopidogrel
C. Ximelagatran
D. Warfarin

Secondary Stroke Prevention: Cardioembolic Stroke

- Cardioembolic stroke is responsible for ~20% of ischemic strokes
- High risk of recurrence if not treated properly
- Underlying cardiac disease*
  - Nonvalvular AF (50%)
  - LVT (33%)
  - Valvular heart disease (25%)
  - Cardiomyopathy with low EF (25%)

*Patients may have more than 1 underlying cardiac condition
EF = ejection fraction; LVT = left ventricular thrombus
Pujadas Capmany R et al. Int J Cardiol. 2004;92(3):129

Cardioembolic Stroke: AF

- Persistent and paroxysmal AF are potent risk factors for recurrent stroke

Risk factors for recurrent stroke in patients with AF

<table>
<thead>
<tr>
<th>Age</th>
<th>CHF</th>
<th>HTN</th>
<th>DM</th>
<th>Prior thromboembolism (TIA or stroke)</th>
</tr>
</thead>
</table>

CHF = congestive heart failure

AHA/ASA 2006 Guideline Recommendations for Antithrombotic Therapy in AF

1. For patients with ischemic stroke or TIA with persistent or paroxysmal (intermittent) AF, anticoagulation with adjusted-dose warfarin (target INR, 2.5; range, 2–3) is recommended (Class I, LOE A)
2. For patients unable to take oral anticoagulants, ASA 325 mg/day is recommended (Class I, LOE A)

Anticoagulation

- Warfarin

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Warfarin (INR goal of 2–3)</th>
<th>Antiplatelet agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke reduction (%)</td>
<td>64 (95% CI 69-74%)</td>
<td>22 (95% CI 6-35%)</td>
</tr>
<tr>
<td>NNT for 1 year for secondary stroke prevention (n)</td>
<td>14</td>
<td>34</td>
</tr>
</tbody>
</table>

- Ximelagatran (investigational)
  - Oral direct thrombin inhibitor that does not require coagulation monitoring
  - SPORTIF-V: 36 mg twice daily was not inferior to warfarin (INR, 2–3) for stroke prevention in AF
  - Potential risk of hepatotoxicity
  - Not approved by FDA for use

FDA = US Food and Drug Administration; INR = international normalized ratio
SPORTIF-V = Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation V
2. Albers GW et al. JAMA. 2005;293(6);690

AHA/ASA 2006 Guideline Recommendations for Antithrombotic Therapy in Acute MI With LVT

1. For patients with an ischemic stroke or TIA caused by an acute MI in whom LVT is identified by echocardiography or another form of cardiac imaging, oral anticoagulation is reasonable, aiming for an INR of 2–3 for at least 3 months and up to 1 year (Class IIa, LOE B)
2. ASA should be used concurrently for ischemic CAD during oral anticoagulant therapy in doses up to 162 mg/day (Class IIa, LOE A)

Sacco RL et al. Stroke. 2006;37(2);577
Guidelines for Symptomatic Extracranial Carotid Occlusive Disease Management

65-Year-Old Woman With 15-Year History of HTN

- On physical examination, a carotid bruit is heard on the left side
- CTA of the neck shows 70%–99% stenosis of the proximal portion of the left ICA

ICA = internal carotid artery

Diagnosis: symptomatic left extracranial ICA stenosis

Which of the following is recommended as first-line treatment of high-grade, symptomatic, extracranial carotid artery stenosis?

A. Extracranial to intracranial bypass
B. Warfarin
C. Carotid endarterectomy
D. Aspirin plus extended-release dipyridamole

Secondary Stroke Prevention: Symptomatic Extracranial Carotid Occlusive Disease

North American Symptomatic Carotid Endarterectomy Trial (NASCET)
- 659 patients with symptomatic stenosis randomized to CEA or medical management
- Only patients with 25-year life expectancy were included
- Perioperative stroke/death rate 5.8%

Stenosis (%) Results
70–99 2-year risk of stroke was 9% with CEA and 26% with medical therapy
50–69 5-year risk of stroke was 15.7% with CEA and 22.3% with medical therapy
<50 No significant benefit of CEA

Carotid Endarterectomy Trialist Collaboration
- Pooled data from European Carotid Surgery Trial and NASCET
- In the CEA arm, benefits were greatest among patients randomized within 2 weeks of symptoms

AHA/ASA 2006 Guideline Recommendations for CEA

1. For patients with recent TIA or ischemic stroke within the last 6 months and ipsilateral severe (70%–99%) carotid artery stenosis, CEA by a surgeon with a perioperative morbidity and mortality rate of <6% is recommended (Class I, LOE A)
2. For patients with recent TIA or ischemic stroke and ipsilateral moderate (50%–69%) carotid stenosis, CEA is recommended depending on patient-specific factors such as age, gender, comorbidities, and severity of initial symptoms (Class I, LOE A)
3. When the degree of stenosis is <50%, CEA is not routinely indicated (Class III, LOE A)
4. When CEA is indicated for patients with TIA or stroke, surgery within 2 weeks is suggested rather than delaying surgery (Class IIA, LOE B)

Sacco RL et al. Stroke. 2006; 37(2):577

AHA/ASA 2006 Guideline Recommendations for Carotid Angioplasty and Stenting

Among patients with symptomatic severe stenosis (>70%) in whom the stenosis is difficult to access surgically, medical conditions are present that greatly increase the risk for surgery, or other specific circumstances exist such as radiation-induced stenosis or restenosis after CEA, CAS is not inferior to endarterectomy and may be considered (Class IIb, LOE B). CAS is reasonable when performed by operators with established periprocedural morbidity and mortality rates of 4% to 6%, similar to that observed in trials of CEA and CAS (Class Ila, LOE B).

Special Note:
The results of the EVA-3S and SPACE studies were published after the 2006 AHA/ASA guidelines became available. EVA-3S and SPACE have added data which support clinical equipoise in relation to CAS. We await the results of Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) to clarify the role of CAS in the management of patients with extracranial occlusive disease.

Sacco RL et al. Stroke. 2006;37(2):377

Guidelines for Symptomatic Intracranial Carotid Occlusive Disease Management

65-Year-Old Woman With 15-Year History of HTN

- Physical examination is unremarkable
- Cerebral vascular diagnostic workup shows no cardiac source of embolism, and both carotid arteries are patent with no evidence of hemodynamically significant stenosis
- Head MRA is ordered, which shows a proximal left MCA stenosis

MCA = middle cerebral artery

65-Year-Old Woman With 15-Year History of HTN

- Diagnosis: large artery intracranial occlusive disease (LAICOD)

Which one of the following is recommended as first-line treatment for large artery intracranial occlusive disease?

A. Antiplatelet therapy
B. Anticoagulant therapy
C. Angioplasty and stenting
D. Extracranial to intracranial bypass

Secondary Stroke Prevention: Symptomatic Intracranial Carotid Occlusive Disease

- Worldwide LAICOD is a common and well-defined stroke subtype
- Certain population groups may be at higher risk for LAICOD

<table>
<thead>
<tr>
<th>Ethnic Group</th>
<th>Reported Frequency of LAICOD in Patients With Stroke (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chinese</td>
<td>35–59</td>
</tr>
<tr>
<td>Korean</td>
<td>56</td>
</tr>
<tr>
<td>South Asian</td>
<td>54</td>
</tr>
<tr>
<td>Thai</td>
<td>47</td>
</tr>
</tbody>
</table>

- Relative risk of intracranial atherosclerotic stroke in the United States
  - Hispanics vs whites: 5.00 (95% CI 1.69 to 14.76)
  - African Americans vs whites: 5.85 (95% CI 1.82 to 18.73)

LAICOD: Risk of Recurrent Cerebral Ischemic Stroke in Key Clinical Trials

- **EC-IC Bypass Study**
  - 1377 patients with symptomatic ICA or MCA stenosis randomized to either surgery or medical management
  - Patients with symptomatic carotid siphon or MCA stenosis had an annual stroke rate of 8%–10%
  - No significant benefit for EC-IC was shown

- **Warfarin-Aspirin Symptomatic Intracranial Disease Trial (WASID)**
  - 569 patients with symptomatic 50%–99% IC stenosis
  - INR goal of 2–3
  - Mean follow up of 1.8 years

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<thead>
<tr>
<th>Outcomes in WASID</th>
<th>ASA (%)</th>
<th>Warfarin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td>20.4</td>
<td>17.0</td>
</tr>
<tr>
<td>Ischemic stroke in the territory of the stenotic vessel</td>
<td>15.0</td>
<td>12.1</td>
</tr>
<tr>
<td>Disabling or fatal ischemic stroke</td>
<td>8.9</td>
<td>6.2</td>
</tr>
</tbody>
</table>


For patients with hemodynamically significant intracranial stenosis who have symptoms despite medical therapies (antiplatelet, statins, and other treatments for risk factors), the usefulness of endovascular therapy (angioplasty and/or stent placement) is uncertain and is considered investigational (Class IIb, LOE C)

AHA/ASA 2006 Guideline Recommendations for Treatment of LAICOD With Endovascular Therapy

Special Note:
The results of the NIH registry on use of Wingspan stent for symptomatic 70%–99% intracranial arterial stenosis were published after the 2006 AHA/ASA guidelines. Based on these results, NIH has funded a study called Stereol vs Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) to study the possible benefit of stenting for symptomatic intracranial artery stenosis.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous stroke or TIA</td>
<td>2.5</td>
</tr>
<tr>
<td>History of HTN</td>
<td>1.6</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.7</td>
</tr>
<tr>
<td>Increasing age (per decade)</td>
<td>1.4</td>
</tr>
</tbody>
</table>

ARR = absolute risk reduction; NNT = number needed to treat; RRR = relative risk reduction

Predicting Stroke Risk in AF: Who Benefits Most? Multivariate Analysis of Pooled Data

Conclusions

- TIA and ischemic stroke are important risk factors for recurrent cerebral ischemia
- Recurrent stroke is preventable
- NSA guidelines for the management of patients with TIA and AHA/ASA guidelines for recurrent stroke prevention are useful clinical tools to reduce the risk of recurrent cerebral ischemia

Appendix I Additional Slides

Polytherapy for Recurrent Stroke Prevention: Opportunity for Reduction of Subsequent Stroke Risk

- 12 meta-analyses (106 studies, 210,926 patients)
- Combination of
  - Diet
  - Exercise
  - ASA (ASA + dipyridamole)
  - Statin (high dose)
  - Antiplatelet therapy (aggressive BP lowering)
- Predicted 5-year major vascular event rate
  - RRR 80% (90%)
  - ARR 20% (22%)
  - NNT 5 (5)
  - Residual 5-year risk 5% (3%)

Predicting Stroke Risk in AF:

- RR = relative risk

Additional Slides
Initiation of Anticoagulation Therapy in AF Patient With Acute TIA or Stroke

- Controversy exists regarding the timing of treatment
- Patients with TIA
  - May receive anticoagulation immediately if not contraindicated by CT, MRI brain, or otherwise
- Patients with ischemic stroke
  - Initiate anticoagulation within 2 weeks of ischemic stroke or sooner depending on CT or MRI brain findings, neurologic examination findings (size and severity of infarct to be considered), and urgency of anticoagulation (eg, mechanical heart valve)
  - Delaying anticoagulation may be reasonable in patients with uncontrolled HTN and large infarcts

Cardioembolic Stroke: Acute MI and LVT

- Acute MI and LVT
  - Stroke and systemic embolism can occur in up to 12% of patients with LVT post MI
  - Risk of LVT is higher in anterior MI
  - Risk of stroke is higher during the first 3 months
  - In one-third of patients, LVT may remain echocardiographically apparent for 1 year after MI

Cardioembolic Stroke: Cardiomyopathy

- Cardiomyopathy
  - Significantly reduced LV systolic function causes relative stasis
  - Annual stroke rate in the Survival And Ventricular Enlargement (SAVE) study
    - 0.8% in patients with EF of 29%–35%
    - 1.7% in those with EF ≤28%
  - No study has definitively proven the efficacy of warfarin or ASA in stroke prevention in patients with cardiomyopathy
  - In practice, patients with thromboembolism suspected of cardioembolic origin with EF below 30% are usually managed with warfarin (INR, 2–3)
  - WARCEF (Warfarin versus Aspirin for Reduced Cardiac Ejection Fraction) study is in progress

AHA/ASA 2006 Guideline Recommendations for Antithrombotic Therapy in Cardiomyopathy

For patients with ischemic stroke or TIA who have dilated cardiomyopathy, either warfarin (INR, 2–3) or antiplatelet therapy may be considered for prevention of recurrent events (Class IIb, LOE C)

Cardioembolic Stroke: Valvular Disease

- PHV
  - Warfarin (INR, 1.8–2.5) versus antiplatelet agents

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Thromboembolism (100 patient-years) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>3</td>
</tr>
<tr>
<td>ASA-dipyridamole</td>
<td>9.8</td>
</tr>
<tr>
<td>Pentoxifylline-ASA</td>
<td>7.9</td>
</tr>
</tbody>
</table>

- Warfarin (INR, 3.0–4.5) vs warfarin plus ASA (100 mg daily)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Annual Rate of Embolic Events or Vascular Death (%)</th>
<th>RR (95% CI)</th>
<th>Bleeding (%)</th>
<th>Increase in Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>9.0</td>
<td>77 (94%–91%)</td>
<td>22</td>
<td>35 (9%–124%)</td>
</tr>
<tr>
<td>Warfarin + ASA</td>
<td>7.0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cardioembolic Stroke: Valvular Disease

<table>
<thead>
<tr>
<th>Valvar Disorder</th>
<th>Comments</th>
<th>Treatment and LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatic valve disease</td>
<td>Recurrent stroke occurs in 30%–65% of patients</td>
<td>Warfarin (INR, 2–3) (Class IIa, LOE C)</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>Most serious form of valve disease, usually necessitates surgery</td>
<td>Antiplatelet agent (Class IIb, LOE C)</td>
</tr>
<tr>
<td>Aortic valve disease</td>
<td>Associated with mitral regurgitation or cardiac failure</td>
<td>Antiplatelet agent (Class IIb, LOE C)</td>
</tr>
<tr>
<td>Mitral annular calcification (MAC)</td>
<td>Associated with and often clinically silent mitral stenosis or regurgitation</td>
<td>Antiplatelet agent (Class IIb, LOE C)</td>
</tr>
</tbody>
</table>


1. For patients with ischemic stroke or TIA who have modern mechanical PHVs, oral anticoagulants are recommended, with an INR target of 3.0 (range, 2.5–3.5) (Class I, LOE B)

2. For patients with mechanical PHV who have an ischemic stroke or systemic embolism despite adequate therapy with oral anticoagulants, ASA 75–100 mg/day in addition to oral anticoagulants and maintenance of the INR at a target of 3.0 (range 2.5–3.5) are reasonable (Class IIa, LOE B)

3. For patients with ischemic stroke or TIA who have bioprosthetic heart valves with no other source of thromboembolism, anticoagulation with warfarin (INR, 2–3) may be considered (Class IIb, LOE C)

PHV = prosthetic heart valve
Sacco RL et al. Stroke. 2006;37(2):577

Cardioembolic Stroke: PFO

- Prevalence in patients 245 years is ~26%
- Atrial septal aneurysm affects ~2%
- 4-year risk of stroke recurrence
  - 2.3% in patients with PFO
  - 15.2% in patients with PFO and atrial septal aneurysm
- Increased risk of stroke in patients with large right-to-left shunt
- Higher prevalence of PFO in patients with cryptogenic stroke
- PFO in Cryptogenic Stroke Study
  - No statistically significant difference in the rate of recurrent stroke in patients with or without PFO or among those treated with ASA or warfarin
  - Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) study and others are comparing percutaneous PFO closure versus medical treatment for recurrent stroke prevention

Cruz-González I et al. Rev Esp Cardiol. 2008;61(7):738

1. Antiplatelet therapy is reasonable to prevent a recurrent event (Class IIa, LOE B)

2. Warfarin is reasonable for high-risk patients who have other indications for oral anticoagulation (Class IIa, LOE C)

3. Insufficient data exist to make a recommendation about PFO closure in patients with a first stroke and PFO

4. PFO closure may be considered for patients with recurrent cryptogenic stroke despite optimal medical therapy (Class IIb, LOE C)

PFO = patent foramen ovale
Sacco RL et al. Stroke. 2006;37(2):577

Guidelines for Carotid Dissection Stroke Management

65-Year-Old Woman With 15-Year History of HTN

- Patient complains of neck pain on the left side
- On physical examination, there is a left partial Horner syndrome (ptosis and miosis)
- Bedside carotid duplex is performed

65-Year-Old Woman With 15-Year History of HTN

- Bedside carotid duplex shows a double lumen in the proximal left ICA (picture above)
- Diagnosis: left extracranial ICA dissection

How should subsequent cerebral ischemia be prevented in a patient with a symptomatic carotid artery dissection?
Secondary Stroke Prevention: Arterial Dissections

- Extracranial arterial dissections
  - Common with atherosclerotic disease
  - Frequent in young patients
  - May be spontaneous or traumatic (neck manipulation, hyperextension, lifting)
  - More commonly detected in extracranial arteries
  - Location includes mostly regions where the arteries are mobile and not anchored
    - Anterior circulation: cervical portion of the ICA
    - Posterior circulation: segments of the vertebral arteries (V1 and V3)

Arterial Dissections: Pathophysiology

- Tear in tunica media results in bleeding in arterial wall
- Blood dissect longitudinally spreading distally and proximally
- Tear of intima permits clots to enter lumen
- Expansion of intramural hemorrhage narrows lumen causing stasis, activation of platelets, and the coagulation cascade
- Main dissection plane can lie between the media and adventitia creating a pseudoaneurysm
- Rupture through adventitia into the intracranial circulation causes subarachnoid hemorrhage

Arterial Dissections: Treatment

- 2003 Cochrane Database review
  - Poor quality studies comparing ASA to warfarin
  - ASA is likely to be effective and safer than warfarin
  - Further studies are needed
- Due to the pathophysiology (red thrombi) most experts recommend anticoagulants
- Annual risk of stroke recurrence in carotid dissection is low (0.3% per year)

AHA/ASA 2006 Guideline Recommendations for Antithrombotic Therapy in Cerebral Artery Dissection

1. For patients with extracranial arterial dissection, use of warfarin for 3 to 6 months or use of antiplatelet agents is reasonable (Class IIa, LOE B)
2. Beyond 3 to 6 months, long-term antiplatelet therapy is reasonable. Anticoagulant therapy beyond 3 to 6 months may be considered among patients with recurrent ischemic events (Class IIb, LOE C)

Secondary Stroke Prevention: Aortic Arch Atheroma

- Prevalence and severity of aortic arch atheroma (AAA) increases with age
- 90% of the cases are stable and AAA progresses slowly over time
- Unclear if AAA is a source of emboli or a marker of an increased risk of atherosclerotic disease
- Risk of stroke is higher in patients with complicated AAAs (i.e., >5 mm in thickness, ulcerated plaque, and mobile)

<table>
<thead>
<tr>
<th>Type of AAA</th>
<th>Odds Ratio of Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple</td>
<td>2.3</td>
</tr>
<tr>
<td>Complex</td>
<td>7.1</td>
</tr>
</tbody>
</table>

Stroke Management in Patients With Aortic Arch Atheroma

AAA Treatment

- New York University Atheroma Group
  - Statin therapy was protective against embolic events
  - No protective effect with warfarin or antiplatelet agents
- Antiplatelet therapy is usually used in patients with stroke or TIA
- No definitive study has determined if warfarin is superior to antiplatelet agents for treatment of AAA
- Aortic Arch Related Cerebral Hazard Trial (ARCH) is comparing clopidogrel + ASA vs oral anticoagulation in preventing brain infarction, brain hemorrhage, MI, peripheral embolism, and vascular death

2. Aortic Arch Related Cerebral Hazard Trial (ARCH).

Carotid Angioplasty and Stenting: Summary of Key Studies II

<table>
<thead>
<tr>
<th>Hypotheses</th>
<th>SAPPHIRE</th>
<th>EVA-3S</th>
<th>SPACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical risk</td>
<td>CAS is not inferior to CEA for high-risk patients</td>
<td>CAS is not inferior to CEA for high-risk patients</td>
<td>CAS is not inferior to CEA for high-risk patients</td>
</tr>
<tr>
<td>Intraprocedural risk</td>
<td>≤ 6%</td>
<td>≤ 6%</td>
<td>≤ 6%</td>
</tr>
<tr>
<td>Degree of stenosis</td>
<td>≥ 70% for CAS</td>
<td>≥ 70% for CAS</td>
<td>≥ 70% for CAS</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>CAS is not inferior to CEA at 5 years</td>
<td>CAS is not inferior to CEA at 5 years</td>
<td>CAS is not inferior to CEA at 5 years</td>
</tr>
<tr>
<td>Primary outcome (CAS) (5 years)</td>
<td>20.1 vs 12.2*</td>
<td>3.9 vs 9.6</td>
<td>6.34 vs 6.84**</td>
</tr>
</tbody>
</table>

*P = 0.04 for noninferiority. **P < 0.05 for noninferiority, CAS = carotid artery stenting

2. The EC/IC Bypass Study Group.
4. SPACE Collaborative Group. Lancet. 2006;368(9543):1239

Treatment of LAICOD Based Upon Key Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NACOTA</td>
<td>22.1</td>
</tr>
<tr>
<td>Warfarin</td>
<td>21.8</td>
</tr>
<tr>
<td>EC-IC Bypass Study Group2</td>
<td>No</td>
</tr>
</tbody>
</table>

NIH registry on use of Wingspan™ stent for 70%–99% intracranial stenosis

<table>
<thead>
<tr>
<th>LAICOD2*</th>
<th>Stroke or death within 30 days or stroke in the territory (1–6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NACOTA3</td>
<td>14</td>
</tr>
<tr>
<td>Warfarin</td>
<td>25</td>
</tr>
</tbody>
</table>

*Major hemisphere occurred more frequently in warfarin vs ASA group (9.3% vs 3.2%; HR 0.40; 95% CI 0.18-0.84; P = 0.01)
**Carotid Occlusion Surgery Study (COSS): is ongoing and testing the hypothesis of benefit for EC-IC bypasses

Secondary Stroke Prevention: Other Specific Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment and LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercoagulability</td>
<td>Anticoagulants if APL syndrome with thrombophilia (class IIa, LOE C)</td>
</tr>
<tr>
<td>- Hyperhomocysteinemia with associated with a risk of stroke</td>
<td></td>
</tr>
<tr>
<td>- Patients undergoing for Stroke Prevention (SYP) study inclusion of anticoagulant treatment after cerebral ischemic event but to avoid</td>
<td></td>
</tr>
<tr>
<td>- Are they subgroups who might benefit from anticoagulation therapy?</td>
<td></td>
</tr>
<tr>
<td>Anticoagulants if APL syndrome (class IIa, LOE C)</td>
<td></td>
</tr>
<tr>
<td>Antiplatelet if APL syndrome (class IIa, LOE C)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment and LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Related Thrombosis</td>
<td>Anticoagulants if APL syndrome (class IIa, LOE C)</td>
</tr>
<tr>
<td>- Brain aneurysm between PFO, PTAM, MTHR, APL, and stroke in adults, new-onset in younger age group</td>
<td></td>
</tr>
<tr>
<td>- No studies examining antithrombotic therapy for secondary prevention</td>
<td></td>
</tr>
<tr>
<td>- Evaluate for antithrombotic therapy</td>
<td></td>
</tr>
</tbody>
</table>

Anticoagulants if APL syndrome (class IIa, LOE C)

APCR = activated protein C resistance; FVL = factor V Leiden; MTHR = methylenetetrahydrofolate reductase C677T mutation; PTGA = prothrombin G20210A mutation

Recurrent Stroke Prevention in Other Cerebrovascular Conditions

Annual stroke rate was 1% in children undergoing hormone therapy.

Postmenopausal hormone therapy is not recommended (Chern 2003; LIE C.)

HS = sickle cell hemoglobin
Sacco RL et al. Stroke, 2006;37(2):377


