Stroke: Incidence and Cost in the United States

- 700,000 new cases yearly
- #3 cause of death
- $43 billion annual health cost (1998)
- 4,400,000 stroke survivors at high risk for recurrence

Most strokes can be prevented
Cost of Stroke

- Stroke severity includes a broad range; about half of survivors unable to walk unaided.
- Acute inpatient costs average $38,000 but are only a fraction of total economic burden (including rehab, long-term care).
- Average lifetime cost of stroke in the U.S. estimated to be $60,000.
Race and Stroke Risk

African-Americans
- Stroke risk increased 1.5-2.5 times.
- Higher prevalence of hypertension.

Hispanic-Americans
- Stroke occurs at younger age (about 6 years earlier than in whites).
- Small subcortical "lacunar" strokes are more frequent.
- Diabetes is an important risk factor.
The Stroke Belt: Stroke Mortality in Black Men

- Fewer than 80 deaths per 100,000 people
- 80 to 129.9 per 100,000
- 130 or more per 100,000
- No data or data unreliable
Causes of Stroke

85% Infarction

60% Cerebrovascular atherosclerosis

20% Penetrating artery disease (lacunes)

15% Cardiogenic embolism

15% Hemorrhage
- Intracerebral
- Subarachnoid

5% Other, unusual causes
Cervical Carotid and Vertebral Arteries
Circle of Willis: Key Collateral Circulation
Vascular Territories of the Cerebral Hemisphere
Causes of Stroke: Cerebrovascular Atherosclerosis

- 85% Infarction
  - Cerebrovascular atherosclerosis: 85%
    - Stenosis (flow reduction)
    - Ulcerated plaque (artery-to-artery emboli)

- 60% Penetrating artery disease (lacunes)

- 20% Cardiogenic embolism

- 15% Hemorrhage
  - Intracerebral
  - Subarachnoid

- 5% Other, unusual causes
Critical Internal Carotid Stenosis
Mechanisms of Ischemia

- Asymptomatic smooth plaque
- Platelet deposits and distal emboli
- Red thrombus with distal embolism
- Occlusive thrombus
Nonstenotic Ulcerated Plaque
Magnetic Resonance Angiography (MRA)

Cervical Carotid Artery

Middle Cerebral Artery
<table>
<thead>
<tr>
<th>FACTOR</th>
<th>INCREASED RISK</th>
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<tbody>
<tr>
<td>Hypertension</td>
<td>X 5-10</td>
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<tr>
<td>Smoking</td>
<td>X 2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>X 1.5</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>X 1.5</td>
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</table>
36% reduction in stroke (p = 0.003)
<table>
<thead>
<tr>
<th>Condition</th>
<th>Goal BP</th>
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<tbody>
<tr>
<td>Uncomplicated</td>
<td>140/90</td>
</tr>
<tr>
<td>Diabetic</td>
<td>135/85</td>
</tr>
<tr>
<td>African-American</td>
<td>135/85</td>
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</table>
Stroke Risk in Smokers

Framingham Data
JAMA 259:1025, 1988

Relative Risk of Stroke

<table>
<thead>
<tr>
<th>No. of Cigarettes Smoked/day</th>
<th>Men</th>
<th>Women</th>
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</thead>
<tbody>
<tr>
<td>10</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>20</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>30</td>
<td>1.6</td>
<td>1.7</td>
</tr>
<tr>
<td>40</td>
<td>1.9</td>
<td>2.0</td>
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</tbody>
</table>

No. of Cigarettes Smoked/day
Stroke Free Survival in Smokers, Nonsmokers and Former Smokers

Survival free of stroke in cigarette smokers (dotted line), nonsmokers (solid line), and former smokers (dashed line), aged 60 years, using Cox proportional hazard regression model, in men and women.
Stroke Facts in Diabetes

- Stroke risk 2 X higher
- Hypertension more prevalent in diabetics
- Strokes occur at younger age
- Risk of death after stroke 2 X higher
- Recovery from stroke less complete
Recent clinical trials of “statins”:

- Reduces stroke by 30% in patients with MI and angina.
- Reversed progression of plaque by ultrasound in early asymptomatic carotid disease.
- Effective in “low-risk” (0.5%/yr stroke rate) patients with modestly elevated cholesterol; not yet tested in high risk patients.

Lipid lowering with “statins” seems sensible to reduce stroke for those with atherosclerotic cerebrovascular disease and LDL cholesterol >130 mg%. 
Transient Ischemic Attack (TIA)

- “Warning strokes”: transient focal ischemia
- Duration: <24 hrs (usually 5 to 10 minutes)
- May occur with any cause of ischemic stroke
- TIA patients have 10 times the risk of ischemic stroke:
  - Risk highest in first 3 months after TIA
  - 35% stroke risk with 3-5 years after TIA
- An opportunity to prevent stroke
Common Manifestations of TIA

Carotid system TIA
- Unilateral weakness
- Unilateral sensory symptoms
- Aphasia
- Monocular vision loss

Vertebrobasilar system TIA
- Bilateral weakness
- Bilateral sensory symptoms
- Diplopia
- Vertigo
- Ataxia without weakness
- Dysphagia
  only in combination; not as isolated symptoms
Established Therapies to Reduce Stroke Due to Cerebrovascular Atherosclerosis

- Control of risk factors
  (especially hypertension, lipids, smoking)
- Antiplatelet agents
  - aspirin
  - ticlopidine / clopidogrel
- Carotid endarterectomy (selected patients)
<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>Daily Dose</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Cyclo-oxygenase inhibition</td>
<td>50-1500 mg</td>
<td>25% stroke reduction</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>ADP receptor blockade</td>
<td>250 mg bid</td>
<td>35% stroke reduction; expensive, rash, diarrhea, leukopenia (1%)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>ADP receptor blockade</td>
<td>75 mg</td>
<td>30% stroke reduction; non-toxic</td>
</tr>
<tr>
<td>Dipyridamole (with aspirin)</td>
<td>Phosphodiesterase inhibition</td>
<td>200 mg bid (25 mg bid)</td>
<td>35-40% stroke reduction; headache in 6%</td>
</tr>
</tbody>
</table>
Effect of Carotid Endarterectomy in Carotid Stenosis: Symptomatic vs. Asymptomatic

- Medical Rx
- Carotid Endarterectomy

Stroke Rate (%/yr)

- Symptomatic Carotid Stenosis (>70%)
- Symptomatic Carotid Stenosis (50-69%)
- Asymptomatic Carotid Stenosis (>60%)
Carotid Endarterectomy for Stroke
Prevention: Summary

- Benefit is established for high-grade (≥70%) symptomatic carotid stenosis.
- Value in moderate (50-69%) symptomatic stenosis is modest and similar to that for asymptomatic carotid stenosis.
- Reduces stroke in asymptomatic carotid stenosis, but magnitude of benefit is small (1%/yr).
- Whether catheter arteriography should routinely precede endarterectomy is controversial.
- Role of carotid angioplasty/stenting undergoing evaluation in trials.
Causes of Stroke:
Penetrating Artery Disease (Lacunes)

- 85% Infarction
- 60% Cerebrovascular atherosclerosis
- 20% Penetrating artery disease (lacunes)
- 15% Cardiogenic embolism
- 15% Hemorrhage - Intracerebral - Subarachnoid
- 5% Other, unusual causes
Lacunar Stroke
Lacunar Infarcts (Small Subcortical Strokes): Summary

- Diagnosis: Clinical syndrome (e.g., pure motor or pure sensory) plus CT/MRI confirmation
- Risk factor management: Hypertension, diabetes
- Carotid stenosis: Present in only 10%
- Rate of occurrence: High (10% yr)
- Antiplatelet agents probably effective
Causes of Stroke: Cardiogenic Embolism

- 85% Infarction
- 60% Cerebrovascular atherosclerosis
- 20% Penetrating artery disease (lacunes)
- 15% Cardiogenic embolism*
- 15% Hemorrhage - Intracerebral - Subarachnoid
- 5% Other, unusual causes
Sources of Cardiogenic Embolism

- Nonvalvular atrial fibrillation (45%)
- Acute MI (15%)
- Rheumatic heart disease (10%)
- Prosthetic cardiac valves (10%)
- Ventricular aneurysm (10%)
- Other, less common sources (10%)
Atrial Fibrillation (AF) Predisposes to Stroke
Mean Onset Age 64, >2 Million People
35% Have Stroke During Lifetime
5% /Yr Stroke Rate
>75,000 Strokes/Yr in U.S.

AF is a marker of 2 million Americans with a six-fold increased risk of stroke.
Stroke: Other, Unusual Causes

*Dissection, migraine, oral contraceptive use in smokers, meningovascular syphilis, cocaine and amphetamine use, associated with prothrombotic states (e.g., sickle cell anemia)
Hemorrhagic Stroke

- 85% Infarction
  - 60% Cerebrovascular atherosclerosis
  - 20% Penetrating artery disease (lacunes)
- 15% Hemorrhage
  - Intracerebral
  - Subarachnoid
- 15% Cardiogenic embolism
- 5% Other, unusual causes
Types of CNS Hemorrhage

- Arteriovenous malformation
- Subdural hematoma
- "Berry" aneurysm (subarachnoid hemorrhage)
- Amyloid angioopathy (lobar)
- "Hypertensive" hemorrhage (deep hemorrhage)
Hypertensive Intracerebral Hemorrhage
Aneurysmal Subarachnoid Hemorrhage
Evaluation of TIA and Ischemic Stroke*

**Step I:**
- CBC, platelet count, PT, PTT, RPR
- Chemistry profile (glucose, cholesterol)
- ECG
- CT Scan

**Step II:**
- Carotid ultrasound
- Echocardiography
- Rhythm (Holter) monitoring if suspicious symptoms

**Step III:**
- Arteriography or MR angiography
- Magnetic resonance imaging
- Special coagulation testing
- Transesophageal echocardiography

* for patients > 50 years old
Acute Stroke Treatment: Salvaging the Ischemic Penumbra
NINDS tPA Study
(NEJM 1995: 333: 1581)

- First proven effective intervention for acute stroke
- Double blind, randomized, 624 patients
- tPA 0.9 mg/kg (max 90mg) infused over 1 hour
- Treatment started <3hrs from stroke onset
- CT documenting absence of hemorrhage
- No anticoagulants or antiplatelet Rx for 24 hrs
<table>
<thead>
<tr>
<th></th>
<th>tPA</th>
<th>Placebo</th>
<th>Absolute Difference</th>
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<tbody>
<tr>
<td><strong>Good Outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barthel 95-100</td>
<td>50%</td>
<td>38%</td>
<td>12%*</td>
</tr>
<tr>
<td>Rankin 0,1</td>
<td>39%</td>
<td>26%</td>
<td>13%</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain hemorrhage</td>
<td>6%</td>
<td>1%</td>
<td>+5%</td>
</tr>
</tbody>
</table>

* 12 extra pts./ 100 given tPA regained normal function
Thrombolytic Therapy
Angioplasty
CT Angiography
**Initial Management of Acute Stroke**

- Determine ischemic vs. hemorrhagic by (CT)
- Consider thrombolytic Rx if <3 hrs from onset
- Assess stroke mechanism
- Systemic management issues:
  - blood pressure
  - oxygenation
  - glucose
  - dysphagia / aspiration precautions
  - D.V.T. prophylaxis
  - fluid status
  - seizures
- Consider aspirin if ischemic stroke, no contraindications
Stroke Prevention: High Risk Patients

- Prior TIA or minor stroke
- Atrial Fibrillation
- Hypertension*
- Asymptomatic Stenosis
- Smoking*

*Patients who have both uncontrolled hypertension and who smoke have a 10-20 fold risk!

Relative Risk

- X 10
- X 5-10
- X 3
- X 2
Summary Diagram of Causes of Stroke

- Intracranial Atherosclerosis
- Carotid Plaque with Arteriogenic Emboli
- Aortic Arch Plaque
- Cardiogenic Emboli
- Flow Reducing Carotid Stenosis
- Atrial Fibrillation
- Valve Disease
- Left Ventricular Thrombi
- Penetrating Artery Disease
Stroke Syndromes: Summary

- Half million new strokes each year
- Effective preventive therapy available to prevent most strokes
- Emphasis must be on prevention

85% Infarction

60% Cerebrovascular atherosclerosis

20% Penetrating artery disease (lacunes)

15% Cardiogenic embolism

15% Hemorrhage
- Intracerebral
- Subarachnoid

5% Other, unusual causes
Established Therapies to Prevent Stroke

- Risk factor control (hypertension, smoking, hyperlipidemia).
- Antiplatelet agents for cerebrovascular disease.
- Anticoagulation for atrial fibrillation and other selected heart diseases.
- Endarterectomy for high-grade symptomatic carotid stenosis (less benefit for moderate symptomatic and asymptomatic stenosis).
### Antithrombotic Therapy for Stroke Prevention: Summary

<table>
<thead>
<tr>
<th>Situation</th>
<th>Recommended</th>
<th>Reasonable Options</th>
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</thead>
<tbody>
<tr>
<td>1. Cerebrovascular diseases</td>
<td></td>
<td></td>
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<tr>
<td>- TIA or stroke</td>
<td>ASA 50-1300 mg/d</td>
<td>Clopidogrel; Ticlopidine</td>
</tr>
<tr>
<td></td>
<td>ASA + ER-DP</td>
<td>ASA + ER-DP</td>
</tr>
<tr>
<td>- TIA or stroke on ASA</td>
<td>Clopidogrel</td>
<td>Ticlopidine</td>
</tr>
<tr>
<td></td>
<td>ASA 325 mg/d</td>
<td>Warfarin INR 1.5-2.5</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- lone AF &lt; 65 yr</td>
<td>ASA 325 mg/d</td>
<td>Warfarin INR 2-3</td>
</tr>
<tr>
<td>- low risk 65-75 yr</td>
<td>ASA 325 mg/d</td>
<td></td>
</tr>
<tr>
<td>- &gt; 75 yr or high risk</td>
<td>Warfarin INR 2-3</td>
<td>ASA if warfarin is</td>
</tr>
<tr>
<td></td>
<td></td>
<td>contraindicated</td>
</tr>
</tbody>
</table>

*ASA = aspirin; ER-DP = Extended release Dipyridamole*