Acute Stroke Treatment and Prevention: Learning the Basic and the Breakthrough Advances

Presented by:
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The following indicates the disclosure declaration information and the nature of those commercial relationships:

Pierre Fayad, MD, PhD: Dr. Fayad is a consultant with Medtronic.

Planning Committee The members of the planning committee, listed below, have no conflicts of interest.

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Pierre Fayad, MD, PhD, Fayad is a consultant with Medtronic.

DISCLOSURE DECLARATION

Acute Stroke Treatment and Prevention:
Learning the Basic and the Breakthrough Advances

Pierre Fayad, MD
Consultant: Medtronic
Series of Activities Available Online
UNMC-CCE offers topics of interest to medical professionals that are available online for CME credit at:
www.unmc.edu/cce/outreach
If you have questions, please contact Sara Weber.

Objectives
- Recognize how to manage acute stroke symptoms and signs
- Identify medical and interventional therapies for acute stroke
- Discuss mechanisms of stroke and strategies for prevention

Stroke General Statistics 2018
Incidence
- 795,000 strokes yearly (610,000 first stroke, 185,000 recurrent)
- 77% ischemic, 10% ICH, 3% SAH
- One stroke every 40 seconds
- Leading cause of disability in adults

Prevalence
- 7.2 million Americans age ≥ 20 years, had a stroke
- US Stroke Prevalence: 2.7%
- Prevalence of least common: Atrial fibrillation - 2%, higher or increasing age
- Hemorrhagic stroke: 6% (4 % in men, 18% in women, age > 60 yrs, and 13% in 60-69 yrs)
- 2015 projections: additional 8.6 million with stroke in US (8.6 million in 2012)

Mortality
- 219,335 Stroke-related deaths yearly (1 of 19 deaths in 2015)
- One stroke-related death in US every 4 minutes
- 33.7% decreased annual stroke death rate (2003-2013)
- 3.6% > 5th US leading cause of death after heart, cancer, lung and accidents
- 6.3 million stroke deaths worldwide (11.8% of deaths)
- Second leading global cause of death

Costs
- $40.1 billion direct ($23.6 billions) & indirect medical costs
- 2035 Projections: $94.3 billions total costs. Most related to age > 85.

Benjamin, E. et al. Circulation. 2018;137:e67-e492. DOI: 10.1161/CIR.0000000000000558; http://circ.ahajournals.org
What Is A “STROKE”?  

**DEFINITION**  
1. Permanent focal brain damage. 
2. Vascular etiology. 
3. Focal neurologic deficit, symptoms or signs. 

Supportive criteria: 
- Clinically lasting > 24 hours (Relative) 
- Imaging/pathology evidence of relevant infarction or hemorrhage. 

Diagnosis is dependent on neurologic deficit and imaging. 

“Clinical syndrome that includes infarction, hemorrhage, and SAH.”


NINDS Classification of CVD III. Stroke 1990, 20:627-680

Stroke Classification and Subtypes

- Hemorrhagic stroke (17%)¹ 
- Intracerebral hemorrhage (59%)²  
- parenchymal or intracerebral hemorrhage (ICH)  
- SAH (41%)² 
- Atherothrombotic large vessel (20%)²  
- Embolism (20%)³  
- Cryptogenic (20%)²

Ischemic stroke (83%)¹


³ Intracerebral hemorrhage (ICH)
Common Etiologies of ICH

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>50%</td>
</tr>
<tr>
<td>Amyloid angiopathy</td>
<td>12%</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>10%</td>
</tr>
<tr>
<td>Tumors</td>
<td>8%</td>
</tr>
<tr>
<td>Prescription and street drugs</td>
<td>6%</td>
</tr>
<tr>
<td>AVMs and aneurysms</td>
<td>5%</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>9%</td>
</tr>
</tbody>
</table>

Charcot-Bouchard Microaneurysm
Intracranial Vascular Malformations

- Cavernous Angioma
- Arteriovenous Malformation
- Venous Angioma
- Capillary Telangiectasia

ICH - General Management

- Monitoring and Management in ICU.
- Consider reversal of anticoagulants, platelets replacement.
- Acute arterial hypertension Management: SBP < 140 mmHg safe.
- DVT prophylaxis: compression, LD anticoagulation.
- Dysphagia screening, nutrition, hydration.
- Hyperglycemia and electrolytes.
- Intracranial hypertension monitoring (CVP target: 5-7mm Hg). Consider EVD drainage LAC, GCS < 9, severe mass effect.
- Hydrocephalus.
- Seizure treatment and NO prophylaxis.
- Surgery and decompression indicated for cerebellar ICH, and possibly deteriorating supratentorial ICA.

Hemphill JC et al. Stroke 2015; 46: 2032-2060

Subarachnoid Hemorrhage (SAH)
Subarachnoid Hemorrhage

Location of Berry Aneurysms

SAH

Symptoms & Diagnosis
Aneurysm Coiling or Clipping

- General Management
  - Monitoring and Management in ICU, specialized stroke centers (>15/year).
  - Nutrition, Hydration (isovolemia)
  - Hyperglycemia and electrolytes (SIADH)
  - Acute arterial hypertension Management, SBP < 160 mmHg.
  - Intracranial hypertension, (target CPP < 70mm Hg)
  - Hydrocephalus
  - DVT prophylaxis
  - Seizure treatment and possible brief prophylaxis.
  - Aneurysm Clipping or coiling:
    - Clipping large (>50 mL) ICH and MCA aneurysms.
    - Coiling: Elderly (>70), poor grade WFNS IV-V.

SAH - General Management
- Monitoring and Management in ICU, specialized stroke centers (>15/year).
- Nutrition, Hydration (isovolemia)
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SAH - Cerebral Vasospasm and Delayed Cerebral Ischemia (DCI)
- A leading cause of death and disability in SAH
- Most frequent 7-10 days after SAH, and resolves after 21 days.
- 20-30% delayed neurologic ischemic deficits.
- Diagnosis: TCD, CTA, MRA, angiography.

Treatment:
- Nimodipine 60 mg qid x 21 days for ALL aSAH.
- Maintain Euvolemia.
- Hypertensive, hypervolemic, hyperosmolar therapy (triple H) for documented DCI.
- Consider local intra-arterial vasodilator (CCB, NO+, papaverine).
- Consider local transluminal angioplasty.
Goals For Acute Stroke Care

- Rapidly triage and identify stroke or other.
- Determine stroke type: Ischemic vs. Hemorrhagic
- Eligibility for "acute stroke therapy"
- Determine size, location, & vascular territory
- Establish plans for efficient management & discharge
- Stabilization & prevention of complications
- Determine etiology & mechanism
- Initiate secondary stroke prevention strategies
- Initiate rehabilitation assessment and therapy

Features of Clinical Situations Mimicking Stroke

<table>
<thead>
<tr>
<th>Condition</th>
<th>Suggestive Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychogenic</td>
<td>Lack of objective findings, neurological findings in a non-vascular distribution, or inconsistent examination</td>
</tr>
<tr>
<td>Seizures</td>
<td>History of seizures, witnessed seizure activity, Post-ictal period</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>History of diabetes, low serum glucose, decreased ICG</td>
</tr>
<tr>
<td>Migraine with aura</td>
<td>History of similar events, preceding aura, headache</td>
</tr>
<tr>
<td>Hypertensive encephalopathy</td>
<td>History of similar events, significant hypertensive, cortical blindness, delirium, seizures</td>
</tr>
<tr>
<td>Wernicke's encephalopathy</td>
<td>History of alcohol abuse, ataxia, ophthalmoplegia, confusion</td>
</tr>
<tr>
<td>CNS abscess</td>
<td>History of drug abuse, endocarditis, medical device implant with fever</td>
</tr>
<tr>
<td>Old tumor</td>
<td>Gradual progression of symptoms, other primary malignancy, onset at onset</td>
</tr>
</tbody>
</table>

Estimated Pace of Neural Circuitry Loss in a Typical Large-Vessel Supratentorial Ischemic Stroke

<table>
<thead>
<tr>
<th></th>
<th>Neurons Lost</th>
<th>Synapses Lost</th>
<th>Myelinated Fibers Lost</th>
<th>Accelerated Aging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per Stroke</td>
<td>1.2 billion</td>
<td>8.3 trillion</td>
<td>7,140 km/4,470 miles</td>
<td>36 years</td>
</tr>
<tr>
<td>Per Hour</td>
<td>120 million</td>
<td>810 billion</td>
<td>914 km/571 miles</td>
<td>5.6 years</td>
</tr>
<tr>
<td>Per minute</td>
<td>1.9 million</td>
<td>14 billion</td>
<td>12 km/7.5 miles</td>
<td>5.1 wks</td>
</tr>
<tr>
<td>Per second</td>
<td>32,000</td>
<td>210 million</td>
<td>200 meters/218 yards</td>
<td>8.7 hrs</td>
</tr>
</tbody>
</table>

Emergent Stroke Care
- Airway, ventilatory support, supplemental oxygen
- Accurate documented Time of onset, or last time known normal (LTKN)
- NIHSS @ Baseline and with neurological change
- Four limb pulses (aortic dissection, PVD)
- Vital signs q15 minutes in ED
- Avoid aggressive control of HTN
  - Except with thrombolysis or thrombectomy
- Monitor cardiac rhythm and 12-lead ECG

Acute Therapies For Ischemic Stroke
- Supportive
- Antithrombotic
- Thrombolytic
- Mechanical thrombectomy
- Neuroprotective???
- Surgical
Supportive Acute Stroke Care

Monitor for potential worsening (ICU/Stroke Unit)
- Neurologic: worsening, recurrence
- Systemic: infectious, metabolic, thrombotic, cardiac

Stabilize vital signs
- Blood Pressure management
- Treat fever aggressively

Hydration
- Replenishment, maintenance of euvolemia

Nutrition
- Screen for dysphagia systematically, particularly high-risk
- Start nutrition early: orally, NG feeds, PEG

Mobility
- Mobilize early
- Fall precautions

Acute Antiplatelet Therapy

CAST (China) CAST Collaborative Group, Lancet 1997;349:1641-1648
- Aspirin 160 mg daily vs. placebo.
- Started within 48 hrs.
- Treatment duration: 1 month.
- Decreases risk of stroke and death at one month.

CHANCE (China) Wang Y et al, NEJM 2012;366:15-19
- TIA/stroke ASA+Clo vs. ASA
- CLO loading 300 mg
- Started within 24 hours.
- Treatment duration 21 days.
- Decreases stroke recurrence, no increased bleeding.

- TIA/stroke ASA+Clo vs. ASA
- CLO loading 600 mg
- Started within 12 hours.
- Treatment duration 90 days.
- Decreases stroke recurrence, increased bleeding = 30 days.

ASA/AHA AIS Guidelines: Acute Anticoagulation

Powers WJ et al. Stroke 2018;49:e46–e99. DOI: 10.1161/STR.0000000000000158
ASA/AHA AIS Guidelines: DVT Prophylaxis

Alteplase (Activase®)
Time: 0-3, 3-4.5 hours

Benefits/Risks of IV tPA For Stroke <3 hrs

For every 100 patients treated

Benefits
• 13 patients cured or almost from neurologic deficits
• 19 patients with improved neurologic deficits

Risks
• 6 have neurologic deterioration from ICH
• 3 patients worsen
• 1 patient severely disabled or dead
MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset (WAKE UP)

- Patients who had evidence of infarction on MRI but no FLAIR signal had a significantly better functional outcome with alteplase than with placebo.
- Excluded: Large stroke > 1/3 MCA territory, or NIHSS > 25.

Mechanical Thrombectomy
Mechanical Thrombectomy Devices

Stent Clot Retrievers
- Solitaire FR (Covidien-Medtronic)
- Trevo XP (Stryker Neurovascular)

Clot Fragmentation and Suctioning
- MAX & ACE (Penumbra)

Functional outcome of patients with ischaemic stroke in trials of endovascular thrombectomy


Mechanical Thrombectomy RCTs

Five RCTs demonstrated clear dramatic benefit + IV thrombolysis at improving functional outcomes, and possibly reducing death when recanalization occurs ASAP within 6-8 hours from symptom onset without major increase bleeding complications

- MR CLEAN (0-6h) (500 pts Netherlands) NEJM 2015; 372:11-20
- ESCAPE (0-12h) (116 pts Canada, US, UK) NEJM 2015; 372:1109-1118
- EXTEND IA (0-6h) (70 pts Australia, NZ) NEJM 2015; 372:2019-2030
- SWIFT PRIME (0-6h) (156 pts US, Europe) NEJM 2015; 372:2283-95
- REVASCAT (0-8h) (206 pts, Spain x4 sites) NEJM 2015; 372:2306-306

Results

- Vessel recanalization: 50-100%
- Neurologic deficit (NIHSS) reduced by half within 24 hours.
- NNT = 2-4 for 1 good functional outcome.
- For every 4 patients treated, one patient is independent at 3 months.
Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct (DAWN)


DEFUSE-3: Example of Perfusion Imaging Showing a Disproportionately Large Region of Hypoperfusion as Compared with the Size of Early Infarction

Favorable Outcome Rates in Early vs. Late Window Thrombectomy Trials

Estimated infarct growth rates in patients with internal carotid artery or middle cerebral artery occlusions.

ASA/AHA AIS Guidelines: Mechanical Thrombectomy
ASA/AHA AIS Guidelines: Mechanical Thrombectomy

Acute L-MCA Occlusion (CTA-COW)

Decompressive Hemi-Cranietomy: CT
Cerebral Vascular Pathologies

- Atherosclerosis
- Cervical, intracranial arterial dissection
- Sinus venous thrombosis
- Moyamoya
- Reversible Cerebral Vasoconstriction Syndrome (RCVS)
- Fibromuscular Dysplasia (FMD)
- Radiation Vasculopathy
- Large Vessel Vasculitis
Lacunar Infarction or Small Vessel Disease

Stroke Most Common Complication of Atrial Fibrillation

All-cause stroke rate with AF is 5%/year
- AF: independent risk factor for stroke
- ~5-fold increase in stroke risk
- ~25% of all strokes caused by AF
- ~50% of cardioembolic strokes caused by AF
- Stroke risk increases with age
- Stroke risk persists with asymptomatic or paroxysmal AF

Cardioembolic Sources

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Medium Risk</th>
<th>Low/No Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial Fibrillation</td>
<td>LV Hypokinesia/Aneurysm</td>
<td>Patent Foramen Ovale (PFO)</td>
</tr>
<tr>
<td>Recent Anterior MI</td>
<td>Bioprosthetic valve</td>
<td>Atrial Septal Aneurysm (ASA)</td>
</tr>
<tr>
<td>Mechanical Valve</td>
<td>Congestive Heart Failure (CHF)</td>
<td>Spontaneous echo contrast</td>
</tr>
<tr>
<td>Rheumatic mitral stenosis</td>
<td>Cardiomyopathy</td>
<td></td>
</tr>
<tr>
<td>Thrombus/Tumor</td>
<td>Endocarditis</td>
<td></td>
</tr>
</tbody>
</table>
Carotid Revascularization: Summary

- CEA, well tested, effective operation in trial patients and public, with surgeons well trained and perform it frequently.
- In symptomatic severe (>70%) > moderate (50-70%) stenosis, CEA INDICATED. (NASCET, EC3T)
- In symptomatic mild stenosis < 50%, CEA NOT INDICATED. (NASCET, EC3T)
- In asymptomatic moderate to severe stenosis, CEA may be considered (ACAS, ACST) but may not be superior to medical therapy.
- Symptomatic Carotid Occlusion with hemodynamic impairment, EC-IC Bypass not superior to medical Rx (COSS)

Carotid Revascularization: Summary

- CAS & CEA equivalent with well trained operators (CREST):
  - CEA higher MI risk,
  - CAS higher stroke risk.
  - CAS riskier in older individuals (>70 y).
- In patients at high-risk CEA, CAS equivalent alternative. (SAPPHIRE)
- In symptomatic severe stenosis: (SPACE, EVA-3S, ICSS)
  - CAS worse than CEA: Peri-procedurally, Age > 70.
  - CAS = CEA in long-term.
- Intracranial stenting higher risk perioperatively than medical treatment (SAAMPRIS) and high restenosis.

Oral Anticoagulation Therapy in Stroke Prevention: Summary

Atrial Fibrillation: Warfarin (64% RRR), or NVKAs very effective for primary and Secondary Stroke Prevention.

Heart Failure with LVEF ≤ 35%: Warfarin not superior to ASA (WARCEF)

2nd Prevention in NON-Cardioembolic Stroke

- Warfarin not superior to ASA (SPIRIT, WARSS, ESPRIT, WASID).
- Rivaroxaban no superior to ASA (NAVIGATE ESUS).
- Dabigatran not superior to ASA (RESPECT ESUS).

Patent Foramen Ovale (PFO):

- Warfarin not superior to aspirin (WARSS)
- PFO closure Amplatzer superior to medical Rx long term (RESPECT, CLOSE, REDUCE [Gore-Holter/Caroflex] or not (CLOSEURE-t, PC-Trial)

Oral Anticoagulation Therapy in Stroke Prevention: Summary

Atrial Fibrillation: Warfarin (64% RRR), or NVKAs very effective for primary and Secondary Stroke Prevention.
Non-Anti-Thrombotic Medical Therapies For Stroke Prevention - Summary
Clear benefit for **statins** in primary (20-30%) and secondary (~16% RRR) stroke prevention with “average” LDL.

**Anti-HTN:** Significant primary & secondary stroke risk reduction (20%-30% RRR). Target SBP < 120 mm (SPRINT)
No benefit (clear harm) from **hormonal replacement** in post-menopausal women.
No benefit from lowering **homocysteine** with B supplements for hyperhomocystinemia in patients with stroke or TIA.

Antiplatelet (AP) Therapy in Stroke Prevention: Summary

- **Combination AP:** ASA+ER-DP (ESPS-2, ESPRIT) more effective (RCT) than ASA in long-term secondary stroke prevention. ASA+CLO not superior to ASA for long-term stroke prevention.
- **Combination AP:** increases risk of ICH and systemic bleeding in 2nd Stroke Prevention.
  - CLO+ASA (MATCH, CHARISMA, SPS-3)
  - ASA+ER-DP (PROFESS)
- **Low-dose ASA** for Primary Stroke Prevention in 10- yrs high-risk, women > men.
**ASA Policy Recommendations**

**Recommendations for the Establishment of Stroke Systems of Care**

Recommendations From the American Stroke Association’s Task Force on the Development of Stroke Systems

Task Force Members

- Lee H. Schapira, MD, Arthur Pasciak, MD, Dee J. Ackerly, MD, HY H. MB, MD,
- Larry H. Goldstein, MD, Richard J. Zorrozua, MD, Timothy J. Hayaphin, MD, CNW, CNS,
- Paul Milet, MD, MPH, M. Stanton, MD, MPH, MHC, M. Grady, MD, MPH, MS, PhD,
- Pamela W. Trac, MD, PhD, Gorlick, MD, Jeffrey Funk, MD, Steven C. Steen, MD, PhD,
- Robert Smith, MD, William Fedorow, MD, Kate R. Horn, BPS, EV,
- Ellen Menden, MHA, Robert J. Adams, MD


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**AHA/ASA Policy Statement**

**Interactions Within Stroke Systems of Care**

A Policy Statement From the American Heart Association/American Stroke Association

- Randall Hughes, MD, FASA, Chair,*, Matt T. Allen, MD, FASA, Co-Chair,*,
- David N. Alexander, MD, Todd J. Cowan, MD, Bar M. Dewhirst, MD,
- Colm F. O’Dowd, MD, FASA; Larry B. Goldstein, MD, FASA,
- Edward C. Jacob, MD, FASA, Stephen A. Myatt, MD, FASA, Neil M. Molloy, FHR,
- Eric D. Peterson, MD, FASA, Robert K. Reiberber, MD, FASA, Jeffrey L. Sears, MD, FASA,
- Lorry Steiner, MD, FASA, David Steinberg, MD, W. Minn, CNN, CNN, CNN,
- HHS establish Stroke System of Care Task Force to provide advice and recommendations regarding implementation of the Stroke System of Care Act and Telestroke services.


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**NE LB 722: “Stroke System of Care Act” (SSCA)**

- Launch date: 1 January 1, 2017 ...

- Hospital Designations:
  - Comprehensive Stroke Centers (CSC)
  - Primary Stroke Centers (PSC)
  - Acute Stroke Ready Hospitals (ASRH)

- HHS to maintain hospital designation list and post on website. Hospitals may not advertise status unless listed with HHS.

- APH and CSC/PSC have protocols and transfer agreement for unavailable therapies.

- Non-ASRH/CSC/PSC have predetermined plans for triage and transfer of acute stroke patients filed annually with HHS.

- EMS to establish pre-hospital care protocols for assessment, treatment, and transport of stroke patients.

- HHS establish Stroke System of Care Task Force to provide advice and recommendations regarding implementation of the Stroke System of Care Act and Telestroke services.

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Critical Issues in Planning

1. First understand what your hospital and team capabilities and goals are and their limitations.
2. Find out what, and how much, is the hospital administration willing to provide startup and continuous support (human, financial and material).
3. Plan according to what you CAN, not what you WISH.
4. Find alternative ways to meet the care of patients, that you cannot provide.
5. Figure out and plan in advance, how to handle patients, triage, treat & transfer.

Strategies to Help Shorten DTN Times (Target: Stroke)

1. Promote pre-notification of hospitals by EMS personnel.
2. Activate entire stroke team with a single call or page.
3. Rapid acquisition and interpretation of brain imaging.
4. Use specific protocols and tools.
5. Premix tPA for high-likelihood candidates.
7. Rapid feedback to the stroke team on performance.


Stroke Care is A Team Sport

- Distribute responsibilities
- Coordination
- Strategies
- Tactics
- Training
- Assess and Improve based on results
APPENDIX

Slides & References

AHA/ASA Guideline

Guidelines for the Management of Spontaneous Intracerebral Hemorrhage

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

The American Academy of Neurology offers the value of this guideline as an educational tool for neurologists.

Endorsed by the American Association of Neurological Surgeons, the Congress of Neurological Surgeons, and the Neurocritical Care Society.

J. Claude Benedict III, MD, MA, FAMA, Chair; Steven W. Goodkin, MD, PhD, Vice-Chair; Colin S. Anderson, MD, PhD, Vice-Chair, Bruce Robinson, MD, PhD, Chair; Janet E. D. Michel, MD, PhD, FAMA; Mary Downie, MD, MSc, FAMA; Michael J. Faug, MD, FAMA; John S. Guille, MD, PhD, FAMA; Charles A. Halpern, MD, FAMA; Brian J. Albert, MD, FAMA; Patrick H. McDowell, MD, FAMA, FAN, PhD, FAMA; Philip A. Smith, MD, FAMA; Megan H. Sato, MD, PhD, Daniel Weis, MD, MSc, on behalf of the American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing, and Council on Clinical Cardiology.

SAH AHA Guideline

Guidelines for the Management of Intracerebral Hemorrhage

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

Enforced by the American Heart Association, the American Stroke Association, and the American College of Cardiology

Connolly ES et al. Stroke 2012;43: 1711-1737


AHA/ASA Guideline

2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke

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

Enforced by the American Heart Association, the American Stroke Association, and the American College of Cardiology


AHA/ASA Guideline

Guidelines for the Primary Prevention of Stroke

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

Enforced by the American Heart Association, the American Stroke Association, and the American College of Cardiology

Connolly ES et al. Stroke 2012;43: 1711-1737


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Stroke Risk Factors

Medical Conditions
- Hypertension
- Cardiac disease
- Atrial fibrillation
- Hyperlipidemia
- Diabetes mellitus
- Carotid stenosis
- Prior TIA or stroke

Non-Modifiable
Age, Gender, Race, Heredity

Behaviors
- Cigarette smoking
- Heavy alcohol use
- Physical inactivity