**Update: Standards in The Management of Acute Ischemic Stroke**

**Stroke Care Guidelines: Why we do what we do**

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May 21, 2013
Financial Disclosure

• None
Stroke Medical Management: the scope of the patients involved

- Headlines vs guidelines

- the rate of rt-PA use in the United States is 1.8% -2.1% of ischemic stroke patients

Getting with the Stroke Guidelines.....
Guidelines of acute stroke care: 

**Objectives**

- Understand how stroke guidelines have been established: *a brief history of medical logic and the guidelines*

- Understand the basic biologic principles underlying acute stroke treatment: *the ischemic penumbra*

- Define the principles and parameters that define the medical management of acute ischemic in regard to:
  - Blood pressure
  - Temperature
  - glcose
  - Oxygenation
  - DVT prophylaxis
  - Management of cerebral edema
  - Early mobility
A brief history of medical logic

Stanley gathered few trophies racing slow rabbits.

SCIENTIFIC METHOD
The basic steps in the scientific method are:

State the problem.
Gather information.
Form a hypothesis.
Test the hypothesis.
Record and analyze data.
State the conclusion.
Repeat the work.
Chronology of acute stroke care Guidelines

- ACCP/AHA Practice Guidelines 1990s
- Brain Attack Coalition Stroke Center definition 2000
- JCAHO Primary Stroke Center Program 2003
Antithrombotic and Thrombolytic Therapy for Ischemic Stroke: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

Maarten G. Lansberg, Martin J. O'Donnell, Pooja Khatri, Eddy S. Lang, Mai N. Nguyen-Huynh, Neil E. Schwartz, Frank A. Sonnenberg, Sam Schulman, Per Olav Vandvik, Frederick A. Spencer, Pablo Alonso-Coello, Gordon H. Guyatt and Elie A. Akl

Chest 2012;141:e601S-e636S
DOI 10.1378/chest.11-2302
AHA/ASA Guideline

Guidelines for the Early Management of Patients With Acute Ischemic Stroke
A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

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

Endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons

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Stroke. 2013;44:870–947
### TABLE 1. Definition of Classes and Levels of Evidence Used in AHA Recommendations

<table>
<thead>
<tr>
<th>Classification</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Class I</td>
<td>Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective</td>
</tr>
<tr>
<td>Class II</td>
<td>Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment</td>
</tr>
<tr>
<td>Class IIa</td>
<td>The weight of evidence or opinion is in favor of the procedure or treatment.</td>
</tr>
<tr>
<td>Class IIb</td>
<td>Usefulness/efficacy is less well established by evidence or opinion.</td>
</tr>
<tr>
<td>Class III</td>
<td>Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Description</th>
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<tbody>
<tr>
<td>A</td>
<td>Data derived from multiple randomized clinical trials</td>
</tr>
<tr>
<td>B</td>
<td>Data derived from a single randomized trial or nonrandomized studies</td>
</tr>
<tr>
<td>C</td>
<td>Consensus opinion of experts</td>
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</tbody>
</table>
Stroke care guidelines

- Pathophysiology

- Medical management
Stroke Subtypes

- Ischemic: 88%
- ICH: 9%
- SAH: 3%

AHA Heart Disease and stroke statistics: 2004; (GCNKSS, FHS, ARIC)
Hemorrhagic Stroke
The most frequent sites of arterial and cardiac abnormalities causing ischemic stroke.

Chest. 2001;119:300S-320S.)

Overview of Stroke: Pathogenesis & Pathophysiology

The Ischemic Penumbra
CBF thresholds for preservation of function and structure

- Normal function
- Functional impairment: biochem. alterations, suppression of EEG and EP, cessation of single cell activity
- Membrane failure
- Single cell necrosis
- Viable tissue
- "Penumbra"
- Infarction

CBF (ml/100g/min) vs. time (min/h)

- 0 min
- 30 min
- 60 min
- 90 min
- 120 min
- 24 h
- 48 h

- Wolf-Dieter Heiss
Ischemic Stroke Pathophysiology

The ischemic **penumbra** is the basis of

i) ‘therapeutic time window’ and acute stroke treatment

ii) medical management of the acute stroke patient
Stroke care guidelines

- Pathophysiology

- Medical management
Acute Stroke Medical Management: The Cornerstone of Care

- Blood Pressure
- Temperature
- Glucose
- Antithrombotic treatment
- Prevention of stroke complications
Case 1

- 68 year-old man
- PMH: HTN, 60 pk/year of smoking, diabetes
- Presented with fluctuating left sided weakness and neglect; on exam NIHSS=5
- Blood glucose 215, EKG NSR
Case 1
Medical management of acute stroke

- Optimal blood pressure?
- Antithrombotic choice?
- Blood glucose management?
Acute Stroke Medical Management: 

**Blood Pressure**

- 77% of patients will have SBP $\geq 139$
- 15% $\geq 184$

- Spontaneous correction within hours

- Aggressive treatment associated with worse outcome

- Loss of autoregulation
Cerebral Autoregulation

Pressure Passive Dilation

Zone of Autoregulation

Vasodilatory Cascade Zone

Autoregulatory Breakthrough Zone

Mean Arterial Pressure (MAP; mm Hg)

Cerebral Blood Flow (CBF; ml/100 g/min)

Medical Management: Ischemic stroke

**blood pressure-hypertension**

In patients with markedly elevated blood pressure who do not receive fibrinolysis, a reasonable goal is to lower blood pressure by 15% during the first 24 hours after onset of stroke. The level of blood pressure that would mandate such treatment is not known, but consensus exists that medications should be withheld unless the systolic blood pressure is >220 mm Hg or the diastolic blood pressure is >120 mm Hg (Class I; Level of Evidence C). (Revised from the previous guideline\(^1\))

....it is generally agreed *that antihypertensive medications should be restarted at ~24 hours for patients* who have pre-existing hypertension and are neurologically stable unless a specific contraindication to restarting treatment is known (Class IIa, Level of Evidence B).
Medical Management: Ischemic stroke \textit{antiplatelet agents}

The oral administration of \textit{aspirin} (initial dose is 325 mg) within 24 to 48 hours after stroke onset is recommended for treatment of most patients (Class I, Level of Evidence A).

The administration of \textit{clopidogrel alone or in combination with aspirin} is not recommended for the treatment of acute ischemic stroke (Class III, Level of Evidence C).

Outside the setting of clinical trials, the intravenous administration of antiplatelet agents that \textit{inhibit the glycoprotein IIb/IIIa} receptor is not recommended (Class III, Level of Evidence B)......
..persistent *hyperglycemia* (>140mg/dL) during the first 24 hours after stroke is associated with poor outcomes, and thus it is generally agreed that hyperglycemia should be treated ...minimum threshold described in previous statements likely was too high, and lower serum *glucose concentrations* (possibly >140 to 185 mg/dL) probably should trigger administration of insulin, similar to the procedure in other acute situations accompanied by hyperglycemia (Class IIa, Level of Evidence C).
Case 1 (cont.)

- Admitted to ICU for close neurologic monitoring
- Placed on aspirin
- 6 hours after admit, developed left hemiplegia with MAP of 88
Medical Management: Ischemic stroke blood pressure-hypotension

In exceptional cases, a physician may prescribe vasopressors to improve cerebral blood flow. If drug induced hypertension is used, close neurological and cardiac monitoring is recommended (Class I, Level of Evidence C).

Drug-induced hypertension, outside the setting of clinical trials, is not recommended for treatment of most patients with acute ischemic stroke (Class III, Level of Evidence B).
Case 1: surgery?

Immediate extracranial-intracranial arterial bypass for treatment of ischemic stroke failed to improve outcomes and was associated with a high risk of intracranial hemorrhage. However, some surgeons have reported favorable results with emergency bypass procedures. (2007)
Case 2

- 73 year old woman onset 12 hours ago of left sided weakness
- PMH: HTN, CAD, atrial fibrillation
- Meds: HCTZ, ASA 81mg
- Exam: afib, 168/86, o2sat-97%
  - Dysarthria, dense L neglect, R gaze deviation dense L hemiparesis
- NIHSS=18
Case 2 (cont.)

- Antithrombotic choice? Anticoagulate?
- Define evidence based routine stroke management
Medical Management Ischemic stroke: *heparin*

*Urgent anticoagulation* with the goal of preventing early recurrent stroke, halting neurological worsening, or improving outcomes after acute ischemic stroke is *not recommended* for treatment of patients with acute ischemic stroke (Class III, Level of Evidence A).

This recommendation may change if additional data demonstrate the usefulness of very early intravenous administration of anticoagulants for treatment of patients with infarctions secondary to large-artery thrombosis or cardioembolism.
Medical Management Ischemic stroke: heparin

2.1. For patients with acute ischemic stroke, we recommend against full-dose anticoagulation with IV, SC, or low-molecular-weight heparins or heparinoids (Grade 1B).

Remarks: Some experts recommend early anticoagulation for various specific stroke subgroups including cardioembolic stroke (atrial fibrillation with rheumatic heart disease, prosthetic heart valves, or intracardiac thrombus), documented intraluminal thrombus, or arterial dissections.
Non-hypoxic patients with acute ischemic stroke do not need supplemental oxygen therapy (Class III, Level of Evidence B).

Assessment of swallowing before starting eating or drinking is recommended (Class I, Level of Evidence B).

If possible, the placement of indwelling bladder catheters should be avoided because of the associated risk of urinary tract infections (Class III, Level of Evidence C).

Early mobilization of less severely affected patients and measures to prevent subacute complications of stroke are recommended (Class I, Level of Evidence C).

Cardiac monitoring is recommended to screen for atrial fibrillation and other potentially serious cardiac arrhythmias. Cardiac monitoring should be performed for at least the first 24 hours (Class I; Level of Evidence B). (Revised from the previous guideline13)
Medical Management Ischemic stroke: *DVT prophylaxis*

*Subcutaneous administration of anticoagulants is recommended* for treatment of immobilized patients to prevent deep vein thrombosis (Class I, Level of Evidence A).

The use of intermittent *external compression devices is recommended for treatment of patients who cannot receive anticoagulants* (Class IIa, Level of Evidence B).
Medical Management Ischemic stroke: *DVT prophylaxis*

Subcutaneous administration of anticoagulants is recommended for treatment of immobilized patients to prevent deep vein thrombosis (Class I, Level of Evidence A).

The use of intermittent external compression devices is recommended for treatment of patients who cannot receive anticoagulants (Class IIa, Level of Evidence B).
It is generally agreed that sources of fever should be treated and antipyretic medications should be administered to lower temperature in febrile patients with stroke (Class I, Level of Evidence C).

..., the utility of induced hypothermia for the treatment of patients with ischemic stroke is not established. At the present time, insufficient evidence exists to recommend hypothermia for treatment of patients with acute stroke (Class III, Level of Evidence B).
Case 2 (cont.)

- Admitted to Neuro ICU
- Neurologic exam stable
- Repeat Head CT 12 and 24 hours later:
Prophylactic administration of anticonvulsants to patients with stroke but who have not had seizures is not recommended (Class III, Level of Evidence C).

Prophylactic anticonvulsant medication should not be used (Class III; Level of Evidence: B). (New recommendation)
Management of malignant edema
Medical Management: Ischemic stroke malignant edema

Major infarctions affecting the cerebral hemisphere or cerebellum are at high risk for edema and increased intracranial pressure. Measures to lessen the risk of edema and close monitoring of the patient for signs of neurological worsening during the first days after stroke are recommended (Class I, Level of Evidence B).

Patients with acute hydrocephalus secondary to an ischemic stroke most commonly affecting the cerebellum can be treated with placement of a ventricular drain (Class I, Level of Evidence B).

Decompressive surgical evacuation of a space occupying cerebellar infarction is a potentially life saving measure, and clinical recovery may be very good (Class I, Level of Evidence B).
Medical Management: Ischemic stroke malignant edema

Although aggressive medical measures, including osmotherapy, have been recommended for treatment of deteriorating patients with malignant brain edema after large cerebral infarction, these measures are unproven (Class IIa, Level of Evidence C). Hyperventilation is a short-lived intervention.

Because of lack of evidence of efficacy and the potential to increase the risk of infectious complications, corticosteroids (in conventional or large doses) are not recommended for treatment of cerebral edema and increased intracranial pressure complicating ischemic stroke (Class III, Level of Evidence A).
Medical Management: Ischemic stroke malignant edema

Decompressive surgery for malignant edema of the cerebral hemisphere may be life-saving, impact of morbidity is unknown. (Class IIa, Level of Evidence B).
Medical Management: Ischemic stroke malignant edema

Walking with a straight base quad cane and ankle/foot orthosis with someone providing hands on assist as needed, able to go up one stair with 25 percent assist. Wheelchair mobility with supervision, bed chair transfers with hands on assistance for safety. Toilet transfers with 25 percent assist, tub transfers with 25 percent assist. Grooming, dressing, toilet hygiene and bathing with standby assist.
Medical Management Ischemic stroke: anticoagulation for atrial fibrillation

For patients with ischemic stroke or TIA with paroxysmal (intermittent) or permanent AF, anticoagulation with a vitamin K antagonist (target INR 2.5; range, 2.0 to 3.0) is recommended (Class I; Level of Evidence A).

4.2.2. In patients with a history of ischemic stroke or TIA and AF, including paroxysmal AF, we suggest oral anticoagulation with dabigatran 150 mg bid over adjusted-dose VKA therapy (target INR range, 2.0 to 3.0) (Grade 2B).

Oral anticoagulation should generally be initiated within 1 to 2 weeks after stroke onset.
Medical Management of Ischemic stroke: Choice of antiplatelet agents

Long-term treatment with aspirin (75-100 mg once daily), clopidogrel (75 mg once daily), aspirin/extended release dipyridamole (25 mg/200 mg bid), or cilostazol (100 mg bid) over no antiplatelet therapy (Grade 1A), oral anticoagulants (Grade 1B), the combination of clopidogrel plus aspirin (Grade 1B), or triflusal (Grade 2B).

4.1.2. Of the recommended antiplatelet regimens we suggest clopidogrel or aspirin/extended release dipyridamole over aspirin (Grade 2B) or cilostazol (Grade 2C).
the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events (Class I; Level of Evidence A).
Aspirin (50 mg/d to 325 mg/d) monotherapy (Class I; Level of Evidence A), the combination of aspirin 25mg and extended-release dipyridamole 200 mg twice daily (Class I; Level of Evidence B), and clopidogrel 75 mg monotherapy (Class IIa; Level of Evidence B) are all acceptable options for initial therapy.

Unfortunately, there have been no clinical trials to indicate that switching antiplatelet agents reduces the risk for subsequent events.
Before PRoFESS

A Not Including Data from the PRoFESS Trial

- Aspirin
  - Relative risk, 0.79
  - (95% CI, 0.67 to 0.92);
  - \( P = 0.003 \)
- Clopidogrel
  - Relative risk, 0.92
  - (95% CI, 0.80 to 1.07);
  - \( P = 0.27 \)

Aspirin-ERDP ----------------- Clopidogrel

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

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

Including Data from the PRoFESS Trial

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

Aspirin

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

Aspirin-ERDP

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

Clopidogrel

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

Kent, DM  Thaler, DE  *NEJM* 359;12 2008
After PRoFESS
In the case of PRoFESS and the tangle of related trials, enlightenment might be expressed simply, as a haiku:

“For stroke prevention, / use an antiplatelet drug. / Treat hypertension.”
An Alternative definition

- Class 0: Things I believe
- Class 0a: Things I believe despite the available data
- Class 1: Randomised controlled clinical trials that agree with what I believe
- Class 2: Other prospectively collected data
- Class 3: Expert opinion
- Class 4: Randomised controlled clinical trials that don't agree with what I believe
- Class 5: What you believe that I don't.

Bleck, T BMJ 2000; 321: 239 (22 July)
Summary: Medical Management

Ischemic stroke

- The penumbral neuron appears to be susceptible to hemodynamic, metabolic, and temperature stress; medical management should be designed to minimize further cell death.

- The cornerstone of medical care for all stroke patients is guideline-driven management of blood pressure, temperature, and blood glucose, and efforts to prevent complications.

- Specific guidelines exist for blood pressure management for both ischemic stroke IC.

- Induced hypertension is not the standard of care (III B).

- Full dose UFH or LMWH Heparin should only be used, if at all, in selected cases in acute stroke (III B).
Summary: *Medical Management*

**Ischemic stroke**

- Subcutaneous administration of anticoagulants is recommended for treatment of immobilized patients to prevent deep vein thrombosis (I A)

- If possible, the placement of indwelling bladder catheters should be avoided because of the associated risk of urinary tract infections (III C)

- A Vitk antagonist or direct thrombin inhibitors should be used for secondary prevention after stroke from atrial fibrillation, (I A) generally w/in 7-14 days
Summary: Medical Management

Ischemic stroke

- Decompressive craniectomy for hemispheric stroke is of uncertain benefit (IIb, C)

- For stroke prevention, use an antiplatelet drug. Treat hypertension