Antithrombotic and Thrombolytic Therapy for Ischemic Stroke*

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)

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This article about treatment and prevention of stroke is part of the Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Grade 1 recommendations are strong and indicate that the benefits do, or do not, outweigh risks, burden, and costs. Grade 2 suggests that individual patients' values may lead to different choices (for a full understanding of the grading, see the "Grades of Recommendations" chapter by Guyatt et al, *CHEST* 2008; 133:123S–131S). Among the key recommendations in this chapter are the following: For patients with acute ischemic stroke, we recommend administration of IV tissue plasminogen activator (tPA) if treatment is initiated within 3 h of clearly defined symptom onset (Grade 1A). For patients with acute ischemic stroke of > 3 h but < 4.5 h, we suggest clinicians do not use IV tPA (Grade 2A). For patients with acute stroke onset of > 4.5 h, we recommend against the use of IV tPA (Grade 1A). For patients with acute ischemic stroke who are not receiving thrombolysis, we recommend early aspirin therapy (Grade 1A). For acute ischemic stroke patients with restricted mobility, we recommend prophylactic low-dose subcutaneous heparin or low-molecular-weight heparins (Grade 1A). For long-term stroke prevention in patients with noncardioembolic stroke or transient ischemic attack (TIA) [*ie*, atherothrombotic, lacunar, or cryptogenic], we recommend treatment with an antiplatelet agent (Grade 1A), including aspirin (recommended dose, 50–100 mg/d), the combination of aspirin and extended-release dipyridamole (25 mg/200 mg bid), or clopidogrel (75 mg qd). In these patients, we recommend use of the combination of aspirin and extended-release dipyridamole (25/200 mg bid) over aspirin (Grade 1A) and suggest clopidogrel over aspirin (Grade 2B), and recommend avoiding long-term use of the combination of aspirin and clopidogrel (Grade 1B). For patients who are allergic to aspirin, we recommend clopidogrel (Grade 1A). In patients with atrial fibrillation and a recent stroke or TIA, we recommend long-term oral anticoagulation (target international normalized ratio, 2.5; range, 2.0 to 3.0) [Grade 1A]. In patients with venous sinus thrombosis, we recommend unfractionated heparin (Grade 1B) or low-molecular-weight heparin (Grade 1B) over no anticoagulant therapy during the acute phase.

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Key words: acute ischemic stroke; antiplatelet agents; aspirin; atrial fibrillation; cardioembolic stroke; cerebral venous sinus thrombosis; clopidogrel; extended-release dipyridamole; heparin; low-molecular-weight heparin; noncardioembolic stroke; oral anticoagulation; stroke prevention; thrombolysis; transient ischemic attack

Abbreviations: ACE = ASA and Carotid Endarterectomy; ADP = adenosine diphosphate; BI = Barthel index; CASES = Canadian Activase for Stroke Effectiveness Study; CAST = Chinese Acute Stroke Trial; CI = confidence interval; CVST = cerebral venous sinus thrombosis; DVT = deep vein thrombosis; ECASS = European Cooperative Acute Stroke Study; ICH = intracerebral hematoma; INR = international normalized ratio; IPC = intermittent pneumatic compression; IST = International Stroke Trial; MCA = main coronary artery; mRS = modified Rankin scale; NIHSS = National Institutes of Health Stroke Scale; NINDS = National Institute of Neurologic Disorders and Stroke; NNT = number needed to treat; OR = odds ratio; PE = pulmonary embolism; PFO = patent foramen ovale; PTT = partial thromboplastin time; PWI = Perfusion Weighted Imaging; r-proUK = recombinant prourokinase; RR = relative risk; RRR = relative risk reduction; rt-PA = recombinant tissue plasminogen activator; SC = subcutaneous; SITS-MOST = Safe Implementation of Thrombolysis in Stroke Monitoring Study; SK = streptokinase; STARS = Standard Treatment with Alteplase to Reverse Stroke; TCD = transcranial Doppler ultrasonography; TIA = transient ischemic attack; TOAST = Trial of ORG 10172 in Acute Stroke Treatment; tPA = tissue plasminogen activator; UFH = unfractionated heparin

Summary of Recommendations

1.1 IV tPA for Acute Ischemic Stroke Within 3 h of Symptom Onset

1.1.1. For eligible patients (see inclusion and exclusion criteria listed below), we recommend administration of IV tPA in a dose of 0.9 mg/kg (maximum of 90 mg), with 10% of the total dose given as an initial bolus and the remainder infused over 60 min, provided that treatment is initiated within 3 h of clearly defined symptom onset (Grade 1A).

Underlying values and preferences: This recommendation places relatively more weight on overall prospects for long-term functional improvement despite the increased risk of symptomatic intracerebral hemorrhage in the immediate peristroke period.

1.1.2. We recommend that patients who are eligible for tPA be treated as quickly as possible within the 3-h time limit (Grade 1A).

Remark: All unnecessary delays must be avoided as the benefits of tPA therapy diminish rapidly over time.

1.1.3. For patients with extensive (more than one third of the middle cerebral artery territory) and clearly identifiable hypodensity on CT, we suggest not using of tPA (Grade 2B).

1.2 IV tPA for Acute Ischemic Stroke Between 3 to 6 h of Symptom Onset

1.2. For patients with acute ischemic stroke of > 3 h but < 4.5 h we suggest clinicians do not use IV tPA (Grade 2A). **For patients with acute stroke onset of > 4.5 h, we recommend against the use of IV tPA** (Grade 1A).

Underlying values and preferences: This recommendation assumes a relatively low value on small increases in long-term functional improvement, a relatively high value on avoiding acute intracranial hemorrhage and death, and a relatively high degree of risk aversion.

1.3 IV Streptokinase for Acute Ischemic Stroke Between 0 and 6 h of Symptom Onset

1.3. For patients with acute ischemic stroke, we recommend against streptokinase (Grade 1A).

1.4 Intraarterial Thrombolysis for Acute Ischemic Stroke

1.4.1. For patients with angiographically demonstrated middle cerebral artery occlusion and without major early infarct signs on the baseline CT or MRI scan, who can be treated within 6 h of symptom onset, we suggest intraarterial thrombolytic therapy with tPA for selected patients in centers with the appropriate neurologic and interventional expertise (Grade 2C).

1.4.2. For patients with acute basilar artery thrombosis and without major CT/MRI evidence of infarction, we suggest either intraarterial or IV thrombolysis with tPA depending on available resources and capabilities (Grade 2C).

2.1 Anticoagulants for Altering Outcomes Among Acute Stroke in Patients Not Eligible for Thrombolysis

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).

2.2 Antiplatelet Agents for Altering Outcomes in Acute Stroke Patients Not Eligible for Thrombolysis

2.2. For patients with acute ischemic stroke who are not receiving thrombolysis, we recommend early aspirin therapy (initial dose of 150–325 mg) [Grade 1A].

2.3 Antithrombotic Therapy for Prevention of Deep Vein Thrombosis and Pulmonary Embolism in Acute Ischemic Stroke

2.3.1. For acute stroke patients with restricted mobility, we recommend prophylactic low-dose SC heparin or low-molecular-weight heparins (Grade 1A).

2.3.2. For patients who have contraindications to

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