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Antithrombotic and Thrombolytic Therapy for Ischemic Stroke*

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

Gregory W. Albers, MD, Chair; Pierre Amarenco, MD; J. Donald Easton, MD; Ralph L. Sacco, MD; and Philip Teal, MD

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; 133:1238–131S). 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 heparins (Grade 1B) over no anticoagulant therapy during the acute phase.

(CHEST 2008; 133:630S–669S)

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 Active 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
anticoagulants, we recommend intermittent pneumatic compression (IPC) devices or elastic stockings (Grade 1B).

3.1 IPC for Deep Vein Thrombosis/Pulmonary Embolism Prophylaxis in Patients With Intracerebral Hematoma

3.1. In patients with an acute intracerebral hematoma (ICH), we recommend the initial use of IPC devices (Grade 1B).

3.2 Heparin for Deep Vein Thrombosis/Pulmonary Embolism Prophylaxis in Patients With ICH

3.2. In stable patients, we suggest low-dose SC heparin as soon as the second day after the onset of the hemorrhage (Grade 2C).

Underlying values and preferences: Given the uncertainty about the risk of heparin in this setting, this recommendation places a relatively high value on reducing the consequences of thromboembolism and a relatively lower value on minimizing the risk of cerebral rebleeding.

4.1 Prevention of Cerebral Ischemic Events in Patients With Noncardioembolic TIA or Stroke: Antiplatelet Drugs vs Placebo or vs an Alternative Antiplatelet Drug

4.1.1. In patients who have experienced a noncardioembolic stroke or TIA (ie, atherothrombotic, lacunar, or cryptogenic), we recommend treatment with an antiplatelet drug (Grade 1A). Aspirin, the combination of aspirin, 25 mg and extended-release dipyridamole, 200 mg bid, and clopidogrel (75 qd) are all acceptable options for initial therapy. We recommend an aspirin dose of 50–100 mg/d over higher aspirin doses (Grade 1B).

4.1.2. In patients who have experienced a noncardioembolic stroke or TIA, we recommend using the combination of aspirin and extended-release dipyridamole (25/200 mg bid) over aspirin (Grade 1A) and suggest clopidogrel over aspirin (Grade 2B).

Underlying values and preferences: The implementation of the recommendation to use the combination of aspirin and extended-release dipyridamole over aspirin may vary based on cost, tolerability, availability, ease of use, and absolute risk.

4.1.3. In most patients with a noncardioembolic stroke or TIA, we recommend avoiding long-term use of the combination of aspirin and clopidogrel (Grade 1B). In those with a recent acute myocardial infarction, other acute coronary syndrome, or a recently placed coronary stent, we recommend clopidogrel plus aspirin (75–100 mg) [Grade 1A]. The optimal duration of dual antiplatelet therapy depends on the specific cardiac indication (see other articles in this supplement).

4.1.4. For patients who are allergic to aspirin, we recommend clopidogrel (Grade 1A).

4.2 Prevention of Noncardioembolic Cerebral Ischemic Events: Oral Anticoagulants

4.2.1. For patients with noncardioembolic stroke or TIA, we recommend antiplatelet agents over oral anticoagulation (Grade 1A).

4.3 Prevention of Cerebral Ischemic Events in Patients Undergoing Carotid Endarterectomy: Antiplatelet Agents

4.3. In patients undergoing carotid endarterectomy, we recommend aspirin (50–100 mg/d) prior to and following the procedure (Grade 1A).

4.4 Prevention of Cardioembolic Cerebral Ischemic Events

4.4.1. In patients with atrial fibrillation who have suffered a recent stroke or TIA, we recommend long-term oral anticoagulation (target INR, 2.5; range, 2.0–3.0) [Grade 1A].

4.4.2. For patients with cardioembolic stroke who have contraindications to anticoagulant therapy, we recommend aspirin at a dose of 75–325 mg/d (Grade 1B).

4.4.3. In patients with stroke associated with aortic atherosclerotic lesions, we recommend antiplatelet therapy over no therapy (Grade 1A). For patients with cryptogenic stroke associated with mobile aortic arch thrombi, we suggest either oral anticoagulation or antiplatelet agents (Grade 2C).

4.4.4. In patients with cryptogenic ischemic stroke and a patent foramen ovale, we recommend antiplatelet therapy over no therapy (Grade 1A) and suggest antiplatelet agents over anticoagulation (Grade 2A).

4.4.5. In patients with mitral valve stenosis or prolapse, who have a history of TIA or stroke, we recommend antiplatelet therapy (Grade 1A).

5.1 Anticoagulation for Cerebral Venous Sinus Thrombosis

5.1. In patients with venous sinus thrombosis, we recommend that clinicians use UFH (Grade 1A).
Ischemic stroke is a syndrome of multiple etiologies and protean clinical manifestations. Atherosclerosis of the arteries, large and small, that supply the brain most commonly causes ischemic stroke. Atherosclerosis of the proximal aorta is also a source of atherogenic brain emboli. Large artery atherosclerotic infarction occurs when there is an impediment to normal perfusion, usually caused by a severe arterial stenosis or occlusion due to atherosclerosis and coexisting thrombosis or artery-to-artery embolism. Microatheroma, lipohyalinosis, and other occlusive diseases of the small penetrating brain arteries are the most frequent causes of small, subcortical “lacunar” infarcts. About 20% of ischemic strokes are due to cardiac embolism, most commonly from atrial fibrillation. Overall, about 30% of ischemic strokes remain cryptogenic despite a reasonably thorough evaluation. Cerebral angiography done within a few hours of cryptogenic stroke typically reveals occlusions of intracranial arteries. Most of these occlusions resolve within a few days, suggesting transient embolic or thrombotic obstruction. Thus, the specific pathogenesis of stroke in individual patients is sometimes difficult to elucidate. Table 1 describes the eligibility criteria for the studies considered in each section of the recommendations that follow.

1.0 Acute Ischemic Stroke: Thrombolytic Therapy in Acute Stroke

The rationale for thrombolytic therapy is based on the recognition that the majority of ischemic strokes are caused by thrombotic or thromboembolic arterial occlusions.1,2 Pathologic and angiographic studies demonstrate the presence of occlusive clot in up to 80% of ischemic strokes.1,3 Thrombotic occlusion may also be responsible for a significant number of events in the 20% of patients without angiographic evidence of occlusion as the thrombus may have lysed spontaneously prior to delayed vascular imaging or the infarct may be due to microthrombus resulting in small-vessel occlusions which escape angiographic detection.

The therapeutic window for rescuing ischemic but still viable brain tissue is attainable for many patients but is challenngingly brief. Neuronal death and brain infarction evolve progressively in a time-dependent fashion determined by both the duration and severity of the ischemic insult.4,5 Therapeutic strategies designed to restore cerebral perfusion in a timely fashion have the potential to limit the cellular, biochemical, and metabolic consequences of cerebral ischemia that ultimately lead to irreversible brain injury. The ultimate goal of early reperfusion therapy is to reduce or prevent brain infarction and thereby minimize the long term disability, neurologic impairment, and stroke-related mortality. The 2001 ACCP Guidelines describe the preclinical evidence and the results of early clinical trials of thrombolysis.6 Table 2 summarizes the results of randomized trials of IV thrombolytic therapies for acute ischemic stroke.

Current Status: The use of IV tissue plasminogen activator (tPA) within the first 3 h of onset of acute ischemic stroke has received regulatory approval in the United States, Canada, Europe, Australia, many Asian countries, as well as several other countries throughout the world. The 1995 landmark report from the National Institute of Neurologic Disorders and Stroke (NINDS) rt-PA Stroke Study Group demonstrated substantial benefit from the careful use of IV tPA in patients with acute ischemic stroke of <3 h duration.7 This ushered in a new era in acute stroke management requiring that stroke be recognized and treated as a time-critical emergency. Although the approved inclusion/exclusion criteria have slight national or regional variations, most countries have adopted protocols based on the principles utilized in the NINDS studies. Despite the potential benefits of thrombolytic therapy, there are considerable obstacles hindering the widespread use of tPA in routine clinical practice. Thrombolytic therapy for acute stroke poses considerable logistical challenges that require a reengineering of stroke care systems to permit widespread access to this treatment.

Thrombolytic therapy for the treatment of acute ischemic stroke has been the subject of intense investigation. In the past several years nine randomized, placebo-controlled trials have been reported using IV recombinant tissue plasminogen activator (rt-PA), streptokinase (SK), or intraarterial recombinant prourokinase (rpro-UK). Metaanalysis of randomized trials of thrombolytic therapy in acute stroke and pooled-data analysis of randomized placebo-controlled trials of tPA vs placebo provides additional evidence for the use of tPA within 3 h of symptom onset.

Concerns regarding the generalizability of clinical trial results and the safety and efficacy of IV tPA therapy in routine clinical practice have been addressed in large formal phase IV studies that have demonstrated results comparable to the NINDS....
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<th>Section</th>
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<td>Acute stroke (symptom onset within 3 h)</td>
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<td>Acute stroke (symptom onset between 3 to 6 h)</td>
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<td>1.3</td>
<td>Acute stroke (symptom onset within 6 h)</td>
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<td>Intraarterial thrombolysis with any agent</td>
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<td>Time (exposure)</td>
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<td>2.2</td>
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<td>2.3.1</td>
<td>Ischemic stroke with restricted mobility</td>
<td>Prophylactic low-dose SC heparin, low-molecular-weight heparins, or the heparinoid danaparoid</td>
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<td>2.3.2</td>
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<td>Randomized controlled trials, cohort studies</td>
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<td>Patients with unstable angina, myocardial infarction, TIA and nonacute stroke</td>
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<td>Death stroke or recurrent stroke</td>
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<td>Death, recurrent stroke</td>
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<td><strong>Symptom onset within 3 h</strong></td>
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<td>NINDS/1995</td>
<td>rt-PA 0.9 mg/kg</td>
<td>Part 1: rt-PA: 144/144; Placebo: 147/147; Part 2: rt-PA: 168/168 Placebo: 165/165</td>
<td>Part 1: 24 h; Part 2: 2-3 mo</td>
<td>78/144 (54%); Placebo: 57/147</td>
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<tr>
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<td>rt-PA 0.9 mg/kg</td>
<td>ITT: rt-PA: 307/307; Placebo: 306/306; TP: rt-PA: 272/272; Placebo: 273/275</td>
<td>3 mo</td>
<td>163/307 (54%); Placebo: 167/306 (55%); TP: rt-PA: 147/272; Placebo: 146/275</td>
<td>1.47 (0.56, 3.87); TP: rt-PA: 1.33 (1.04, 2.04); Placebo: 1.33 (1.04, 2.04)</td>
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<td>Placebo</td>
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<td><strong>Symptom onset within 3 to 9 h</strong></td>
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<td>Hacke et al¹⁰/2004</td>
<td>Desmoteplase 25 mg; Placebo: 37.5 mg; Part 2: Desmoteplase 62.5 µg/kg, 90 µg/kg or 125 µg/kg</td>
<td>ITT: Desmoteplase: 30/30; Placebo: 16/16; TP: Desmoteplase: 45/45; Placebo: 11/11</td>
<td>3 mo</td>
<td>128/307 (42%); Placebo: 122/306 (40%); TP: rt-PA: 115/272; Placebo: 106/275</td>
<td>1.79 (0.51, 6.36); TP: rt-PA: 3.47 (0.56, 21.65); Placebo: 0.55 (0.06, 5.34)</td>
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<td>Placebo</td>
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<td>Furlan et al¹⁰⁸/1999</td>
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<td>ITT: Desmoteplase: 28/28; Placebo: 5/5; TP: Desmoteplase: 19/19; Placebo: 6/6</td>
<td>90 d</td>
<td>13/29 (45%); Placebo: 2/25 (25%); TP: 1.79 (0.51, 6.36); Placebo: 1.79 (0.51, 6.36); TP: 1.79 (0.51, 6.36)</td>
<td>0.49 (0.06, 4.92); Placebo: 1.79 (0.51, 6.36); TP: 1.79 (0.51, 6.36); Placebo: 1.79 (0.51, 6.36)</td>
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* This study only reports the "Favorable Clinical Outcome" results. Results on favorable outcome are presented as "Favorable Clinical Outcome" on the study. They represent an 8-point improvement on NIHSS (0 to 1), mRS (0 to 2), and BI (75 to 100).

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<th>mRS</th>
<th>NIHSS</th>
<th>Favorable Outcome\†, No./Total (95% CI)</th>
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<td>Symptom onset within 6 h</td>
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<tr>
<td>Clark et al(^4)*2000</td>
<td>ATLANTIS A</td>
<td>rt-PA: 71/71; Placebo: 71/71</td>
<td>90 d</td>
<td>rt-PA: 33/71 (46%)\‡; Placebo: 35/71 (49%); RR: 0.94 (0.67, 1.33)</td>
<td>rt-PA: 25/71 (35%); Placebo: 18/71 (25%); RR: 1.39 (0.84, 2.31)</td>
<td>rt-PA: 15/71 (23%); Placebo: 5/71 (7%); RR: 3.20 (1.24, 8.26)</td>
<td>rt-PA: 62/71 (87.3%); Placebo: 54/71 (76.1%); RR: 1.15 (0.98, 1.34)</td>
<td>Death and dependency results taken from Wardlaw J et al. Thrombolysis for acute ischaemic stroke. The Cochrane Library 2006, Issue 3</td>
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| Hacke et al\(^5\}/ECASS I | rt-PA 1.1 mg/kg | ITT: rt-PA: 313/313; Placebo: 307/307; TP: rt-PA 247/247; Placebo: 264/264 | 90 ± 14 d | ITT: rt-PA: 112/313; (36%)\‡; Placebo: 90/307 (29%); RR: 1.22 (0.97, 1.53) | TP: rt-PA 101/247 (41%); Placebo: 77/264 (29%); RR: 1.40 (1.10, 1.78) |     | | \*
| Hacke et al\(^5\}/ECASS II | rt-PA 1.1 mg/kg | ITT: rt-PA: 409/409; Placebo: 391/391 | 90 d | rt-PA: 204/409 (50%); Placebo: 179/391 (46%); RR: 1.09 (0.94, 1.26) | rt-PA: 165/409 (40%); Placebo: 143/391 (37%); RR: 1.10 (0.93, 1.32) | rt-PA: 43/409 (11%); Placebo: 42/391 (11%); RR: 0.98 (0.64, 1.46); Placebo: 211/391 (53%); RR: 0.89 (0.77, 1.02) | Death and dependency results taken from Wardlaw J et al. Thrombolysis for acute ischaemic stroke (Review). The Cochrane Library 2006, Issue 3 |

*ITT = intention-to-treat; TP = target population.
\*Favorable outcome.
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<th>BI</th>
<th>mRS</th>
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<td>95</td>
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\(\delta\) Favorable outcome.
\(\delta\) 95; mRS, 0–1.
\(\delta\) NIHSS, 0–1.
Trials. Finally, numerous case series and registries using protocols derived from the NINDS trials have been generally favorable.

Our current recommendations are based on the clinical trial inclusion criteria of time from symptom onset to treatment and on the accepted importance of early treatment. Differences in fibrin specificity, pharmacokinetic and pharmacodynamic properties prevent the ready extrapolation of trial results with IV tPA to other agents, doses, or routes of administration.

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

Metaanalysis Data for Treatment < 3 h: The Cochrane stroke group has evaluated the time to treatment effect for thrombolysis in acute stroke. The main Cochrane metaanalysis includes studies that used either tPA (NINDS, European Cooperative Acute Stroke Study [ECASS], and ECASS II) or SK (MAST-I, MAST-E, and ASK) within the first 3 h after symptom onset. The NINDS trial contributed > 50% of treated patients to this metaanalysis.8,9 Thrombolytic therapy within 3 h of symptom onset significantly reduced the number suffering the combined end point of death or dependency: 55.2% thrombolytic-treated patients died or were dependent compared with 68.3% of those allocated to control (odds ratio [OR], 0.58; 95% confidence interval [CI], 0.5–0.7; p < 0.0000; absolute risk reduction, 13.1%). There was a nonsignificant excess of deaths in the thrombolysis-treated group 22.3% vs 20.7% in control patients (OR, 1.11; 95% CI, 0.84–1.47). Overall there were 126 fewer dead or dependent stroke patients for every 1,000 thrombolysis-treated patients within 3 h of symptom onset. The Cochrane metaanalysis restricted to all trials using tPA (NINDS, ECASS I, and ECASS II) and more relevant to current practices demonstrated even more favorable results: 140 fewer dead or dependent per 1,000 tPA-treated patients (OR, 0.55; 95% CI, 0.42–0.72) with a nonsignificant trend toward fewer deaths (OR, 0.92; 95% CI, 0.65 to 1.30).

Pooled Data Analysis: The investigators of the large tPA trials (ATLANTIS A and B, ECASS I and II, and the NINDS trials) conducted a pooled analysis using original individual patient data (n = 2,775) from these six randomized trials comparing IV tPA and control.10 An adjusted multiple logistic regression model demonstrated a relationship between onset-to-treatment time and treatment effect. There was substantial evidence of benefit for tPA therapy delivered within the first 180 min and evidence of declining benefit up to 270 min after symptom onset. Efficacy outcomes were measured utilizing the National Institutes of Health Stroke Scale (NIHSS) as measure of neurologic deficit, the modified Rankin Scale (mRS) as measure of global disability, and the Barthel Index (BI) as measure of independence in activities of daily living. Favorable outcome was defined by the NIHSS, mRS, and BI dichotomized to evaluate minimal or no poststroke disability. The OR for favorable 3-month outcome for patients treated with tPA compared to placebo was 2.8 (95% CI, 1.8–4.5) when tPA was given in the first 90 min, 1.6 (1.1–2.2) for 91–180 min, and 1.4 (1.1–1.9) for 181–270 min. The benefit of IV tPA therapy becomes small and lacks significance (OR, 1.2; 95% CI, 0.9 to 1.5) for patients treated between 271 and 360 min. The rate of clinically significant parenchymal hematoma defined as a dense space-occupying blood clot resulting in early neurologic deterioration or death was 5.9% with tPA compared to 1.1% in placebo-treated patients (p < 0.01). The 90-day mortality rate in patients with symptomatic intracerebral hematoma (ICH) was not significantly associated with onset to treatment time (p = 0.71) or baseline stroke severity (p = 0.10). This analysis demonstrates that earlier treatment is strongly associated with greater benefit and that patients should be treated as quickly as possible. It also suggests that a diminishing small benefit may persist for up to 4.5 h.

Time-to-Treatment Effect: A consistent and powerful time-to-treatment effect on clinical outcome has been demonstrated in both the NINDS study (see below) as well as in the pooled analysis.10,11 Outcomes are better with early treatment. The practice implications of this observation are profound. Systems of emergency stroke care must be optimized to provide for rapid patient access, evaluation, imaging, and treatment.

Individual Trials of tPA Within 3 h: Four large-scale trials using different doses, therapeutic windows, and treatment protocols have evaluated IV tPA: the NINDS rt-PA study7 the ECASS-I,12 the ECASS II,13 and the ATLANTIS rt-PA (Alteplase) Acute Stroke Trial.14,15 The 2004 ACCP Guidelines include a detailed summary of these trials.16 Safety and efficacy data are summarized in Table 2.

Only the NINDS rt-PA study exclusively included patients treated within 3 h of symptom onset and this trial was the only study to clearly demonstrate efficacy on the primary end points.7 In NINDS, the benefits of tPA were consistent regardless of patient age, stroke subtype, stroke severity, or prior use of aspirin. Patients with severe neurologic deficits measured by the baseline NIHSS were less likely to have
a good outcome, regardless of treatment. A subgroup analysis of patients ≥ 75 years old with an initial NIHSS of > 20 (20 points is a severe stroke typically presenting with severe motor, sensory, visual, and language or behavioral deficits) demonstrated a reduction in death or severe disability with tPA compared with placebo.\textsuperscript{17} This overall benefit occurred despite the increased risk of symptomatic ICH in patients with severe strokes (adjusted OR, 4.3; 95% CI, 1.6–11.9).

There were differences in baseline NIHSS scores between tPA-treated and placebo-treated patients in the NINDS study. These differences increased the number of patients with favorable outcomes in the tPA group treated between 91–150 min and reduced favorable outcomes with tPA in the 0–90 min group. Analysis of the NINDS data, adjusted for the baseline NIHSS, demonstrated an effect of onset-to-treatment time for a favorable 3-month outcome: the adjusted OR for a favorable 3-month outcome in tPA-patients treated within the first 90 min was 2.11 (95% CI, 1.33–3.35) compared to 1.69 (95% CI, 1.09–2.62) for patients treated between 91 and 181 min.\textsuperscript{11} There was no onset-to-time of treatment effect on the incidence of ICH.

A formal independent reanalysis of the NINDS data commissioned to address concerns about the potential impact of baseline variables found that the adjusted tPA to placebo OR of a favorable outcome was 2.1 (95% CI, 1.5–2.9), despite the differences in baseline severity and despite the increased risk of symptomatic ICH.\textsuperscript{15} The clinical impact of symptomatic ICH is of course integrated into the overall assessment of favorable outcome.

**Phase IV Studies:** Three large formal prospective Phase IV studies have examined outcomes with use of tPA in NINDS-derived protocols restricted to a 3-h treatment window in clinical practice. The Standard Treatment With Alteplase to Reverse Stroke (STARS) study included 389 patients from 57 medical centers in the United States (24 academic and 33 community).\textsuperscript{19} The Canadian Activase for Stroke (CASES) enrolled 1,132 patients from 57 medical centers in Canada (25 academic and 35 community).\textsuperscript{20} Both STARS and CASES demonstrated that low rates of symptomatic intracerebral hemorrhage (3.3% in STARS and 4.6% in CASES) could be obtained using tPA in broad clinical practice settings. These studies are reviewed in the 2004 ACCP guidelines.\textsuperscript{16}

The most recent large phase IV trial was the European SITS-MOST Study (Safe Implementation of Thrombolysis in Stroke Monitoring Study).\textsuperscript{21} This prospective, open, monitored observational cohort study was mandated by the European Agency of Medicinal Products as a condition for permanent licensing of tPA in the European Union. A total of 6,483 patients were treated with IV tPA between 2003 and 2006 making SITS-MOST the largest phase IV study evaluating clinical safety of tPA use in acute ischemic stroke. In addition to conventional NINDS tPA exclusions, SITS-MOST also excluded patients if they were > 80 years of age or if their baseline NIHSS score was > 25 points. The primary outcome measures were symptomatic intracranial hemorrhage (defined as a type 2 parenchymal hematoma exceeding 30% of the infarct area with mass effect combined with clinical worsening of ≥ 4 points on the NIHSS scale) and death. The incidence of symptomatic intracerebral hemorrhage as defined was 1.7%. Applying the Cochrane/NINDS definitions for symptomatic ICH of any bleeding plus any neurologic worsening, the incidence of symptomatic ICH was 7.3% at 7 days. The overall mortality rate was 11.3% compared to 17.3% in the pooled controlled clinical trials data. Although SITS-MOST defined patient eligibility more stringently than either CASES or STARS, this very large study provides considerable reassurances regarding the safety and effectiveness of tPA in clinical practice both in experienced and inexperienced centers.

The results of these three large formal phase IV studies demonstrate that IV tPA can be given with safety and clinical outcomes comparable to those demonstrated in the NINDS trial and with a trend to lower rates of symptomatic ICH. These studies also demonstrated that comparable results were obtained in both academic centers and community hospitals and in both experienced and inexperienced sites providing protocols are in place and adhered to.

**Published Reports From Routine Clinical Practice:** Published reports of the use of tPA in routine clinical experience have generally been favorable with reported rates of symptomatic ICH usually < 7%.\textsuperscript{22–25} The largest multicenter survey of the use of tPA in clinical practice reported a 6% symptomatic ICH rate in 1,205 patients analyzed both retrospectively and prospectively.\textsuperscript{26} Logistic regression models identified age, stroke severity, elevated glucose, low platelets, and early major CT changes as predictors of symptomatic ICH. Strict adherence to protocols and experience are important to ensure appropriate use and adequate safety. Increased rates of symptomatic ICH associated with protocol violations have been reported by several groups.\textsuperscript{27,28} A survey of community experience in 29 Cleveland area hospitals reported a symptomatic ICH rate of 15.7% associated with protocol violations in 50% of the 70 patients.\textsuperscript{29} This exceptionally high rate of ICH underscores the need for close adherence to
protocol guidelines and the importance of experience and expertise. A subsequent report from the Cleveland area hospitals has demonstrated that training and better adherence to NINDS-based protocols can result in reduction in the rates of ICH to acceptable levels.

Resource Implications

A cost-effectiveness analysis based on data from the NINDS trial concluded that tPA was economically dominant—both more effective and cost saving compared with not using tPA. The cost savings were attributable to reduced length of hospital stay seen for tPA patients in the trial, as well as reduced projected use of rehabilitation and nursing home resources. A similar study, based on the NINDS project, projected use of rehabilitation and nursing home care for tPA patients in the trial, as well as reduced long-term care. Thus the economic case for tPA is compelling only in integrated health systems where the increased risk of symptomatic intracerebral hemorrhage in the immediate peristroke period is not perceived to be technically surmountable, the effort required for what is often a small number of eligible patients is not perceived to be good use of resources. Further, the costs of tPA are borne by the acute care hospital, which does not benefit from cost savings due to decreased need for long-term care. Thus the economic case for tPA is compelling only in integrated health systems engaged in the care continuum.

Recommendation

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 > 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. The following criteria determine eligibility for treatment.

Inclusion Criteria: Age ≥ 18 years, clinical diagnosis of stroke with a clinically meaningful neurologic deficit, clearly defined time of onset of < 180 min before treatment, and a baseline CT showing no evidence of intracranial hemorrhage.

Exclusion Criteria: Minor or rapidly improving symptoms or signs, CT signs of intracranial hemorrhage, a history of intracranial hemorrhage, seizure at stroke onset, stroke or serious head injury within 3 months, major surgery or serious trauma within 2 weeks, GI or urinary tract hemorrhage within 3 weeks, systolic BP > 185 mm Hg, diastolic BP > 110 mm Hg, aggressive treatment required to lower BP, glucose < 50 mg/dL or > 400 mg/dL, symptoms of subarachnoid hemorrhage, arterial puncture at a noncompressible site or lumbar puncture within 1 week, platelet count < 100,000/mm³, heparin therapy within 48 h associated with elevated activated partial thromboplastin time, clinical presentation suggesting post-myocardial infarction pericarditis, pregnant or breastfeeding women, anticoagulation due to oral anticoagulants (international normalized ratio [INR] > 1.7).

Recommendation

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).

Remarks: All unnecessary delays must be avoided as the benefits of tPA therapy diminish rapidly over time. Analysis of data from the NINDS trial and from the pooled analysis show that benefits of therapy are optimal when treatment is given early and decline progressively over time. Public awareness, rapid transport to hospital, immediate emergency department assessment, activation of the local stroke team, rapid access to CT or MRI scans, and clearly
defined stroke protocols serve to minimize the stroke onset-to-treatment times and promote optimal prospects for recovery. Hospitals should monitor door-to-treatment times to improve performance.

Physicians with experience and skill in stroke management and the interpretation of CT scans should supervise treatment. Some experts advise that, if possible, efforts should be made to demonstrate a large artery intracranial occlusion using modern neuroimaging techniques prior to administration of tPA. Treatment, however, should be administered as rapidly as possible to maximize benefits. Treatment should not be unduly delayed in order to facilitate vascular imaging. Administration of thrombolytic therapy as well as monitoring for and management of potential complications requires adequate hospital facilities and personnel. Following tPA administration, BP should be closely monitored and kept below 180/105 mm Hg; antithrombotic agents, including aspirin, should be avoided for 24 h.

1.1.3 Patients With Pretreatment CT Signs of Major Infarct (Clear Evidence of Extensive Hypodensity or Substantial Edema and Mass Effect)

A technically adequate head CT scan (or MRI) is required prior to administration of thrombolytic therapy to exclude brain hemorrhage and nonischemic diagnoses. The baseline CT scan is also sensitive for detection of early signs of cerebral infarction. Subtle or limited signs of early infarction on the CT scan are common even within the first 3 h of stroke evolution. These signs include blurring of the internal capsule, loss of clarity of the lentiform nucleus, loss of differentiation between cortical gray matter and subcortical white matter (eg, loss of the insular ribbon), and mild sulcal effacement. In the NINDS trial, the pretreatment CT was utilized simply to rule-out ICH and the detection of early infarct signs was not an exclusion criterion for enrollment. A post hoc CT analysis found early ischemic changes in 31% of baseline scans. After adjusting for NIHSS, there was no association between the presence of early ischemic changes and the occurrence of symptomatic ICH in the tPA-treated group (p = 0.22).

In contrast to minor signs, the detection of major early ischemic change on the baseline CT, defined as the presence of substantial mass effect or well-defined hypodensity involving greater than one third of the middle cerebral artery territory, is associated with poor outcomes, regardless of therapy, and is associated with an increased risk of ICH following thrombolysis. The NINDS protocol did not exclude patients with early infarct changes on baseline CT scans, regardless of the extent of ischemic abnormalities. The investigators have subsequently reported the impact of treatment with tPA in patients with various CT abnormalities.36 Major early infarct signs on CT, defined as the presence of brain edema or mass effect, were associated with an increased risk of symptomatic ICH in tPA-treated patients (OR, 7.8; 95% CI, 2.2–27.1). Subsequent reanalyses of the NINDS CT scans, including the application of the ASPECTS score (a validated systematic approach for the evaluation of early infarct signs), did not detect evidence for a modification of treatment effect based on early CT changes.37,38

Several other randomized trials (ECASS I, ECASS II, PROACT II, ATLANTIS) excluded patients with major early infarct changes, defined as parenchymal hypodensity greater than one third of the main coronary artery (MCA) territory. The ECASS I investigators reported an increased rate of clinically significant hemorrhagic transformation in tPA-treated patients enrolled despite the presence of major early ischemic changes on baseline CT (protocol violators) compared to those without major early CT findings. Patients with major early infarct signs who were treated with TPA had a higher rate of death and disability compared with placebo-treated patients. A secondary analysis of the ECASS II study reported that the extent of hypodense changes on the baseline CT was an independent risk factor for the occurrence of symptomatic ICH (OR, 2.64; 95% CI, 1.59–4.39).39 However, these investigators did not report the magnitude of the effect of treatment on death and dependency in this subgroup of patients.

At present the significance regarding the safety and efficacy of tPA in patients with major early ischemic changes on CT is controversial.40–42 Only 2% of the patients in the NINDS study had extensive hypodensity (greater than one third of the MCA territory) on the pretreatment CT scan.37 As clearly identifiable and extensive hypodensity likely reflects irreversible tissue injury and potentially carries a substantial increase in the risk of symptomatic ICH accompanied by neurologic worsening or death, we caution against administration of thrombolytic therapy for this very small subset of patients and clinical judgment is required.

Recommendation

1.1.3. For patients with extensive (more than one third of the middle cerebral artery territory) and clearly identifiable hypodensity on CT, a significant infarct is already established. The benefits/risks of IV tPA are uncertain, and we suggest not using tPA in this situation (Grade 2B).

Remarks: Minor ischemic changes on CT are
commonly present and subtle or small areas of hypodensity or loss of gray-white distinction, obscuration of the lentiform nucleus, or the presence of a hyperdense artery are not a contraindication to treatment. Clinical judgment must be exercised when deciding the potential risks and benefits of tPA treatment in patients with large and very clearly established infarcts on pretreatment CT imaging.

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

Metaanalysis Data: The Cochrane Stroke Review Group metaanalysis reported that IV tPA given within the first 6 h of symptom onset (n = 2,764) showed a significant (though less robust than < 3 h treatment) benefit with a reduction in death or dependency from 57% in the control group compared to 51% in the tPA-treated group (OR, 0.79; 95% CI, 0.68–0.92; p = 0.002). The benefits with a 6-h window occurred despite the increase in symptomatic intracranial hemorrhage from 3% in controls to 10% in treated patients (OR, 3.2; 95% CI, 2.4–4.3). The benefit of tPA given within 6 h is a reduction of 55 dead or dependent patients for every 1,000 treated.43

A metaanalysis by Ringelb et al44 of patients treated with tPA in the 3- to 6-h time window from the ATLANTIS, ECASS, and ECASS II reported an OR of 0.79 (95% CI, 0.66–0.96) in favor of tPA for reducing death and dependency (mRS, 3 to 6). The pooled analysis of patient data from the large 3- to 6-h window tPA trials (ATLANTIS, ECASS, and ECASS II) demonstrated a small and progressively declining but significant beneficial effect of tPA for up to 270 min following symptom onset and a nonsignificant trend of benefit between 271–360 min. Safety and efficacy results from these trials are summarized in Table 2; the individual trials are reviewed in the 2004 ACCP guidelines.16

Recommendation

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 relatively less weight to small increases in long-term functional improvement than to avoidance of acute intracranial hemorrhage and death, and a relatively high degree of risk aversion. For highly selected patients, such as those with major neurologic deficits from suspected basilar artery thrombosis or in the setting of compelling clinical and neuroimaging criteria (see Section 1.6 below), IV tPA may be considered beyond the 3-h limit.

Remark: Further data are required to identify patients in the 3- to 6-h treatment window who are most likely to benefit or be harmed by IV tPA. Two clinical trials, ECASS III and IST 3, are in progress evaluating IV tPA in the 3- to 4.5-h and 6-h windows, respectively. Acute basilar artery occlusion is often given special consideration. In the absence of reperfusion, basilar artery thrombosis carries an extremely high fatality rate. In the absence of adequate trial data, many stroke experts will treat selected patients with basilar occlusion beyond the 3-h window based on compelling clinical circumstances, the use of advanced neuroimaging criteria, and expert evaluation.

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

Metaanalysis: The Cochrane analysis reported a significant increase in the number of symptomatic (including fatal) ICH hemorrhages in the SK vs control treatment trials (OR, 5.20; 95% CI, 3.25–8.32). There was no effect on death or dependency at the end of follow-up for either SK without aspirin vs control (OR, 0.94; 95% CI, 0.72–1.24) or SK plus aspirin vs aspirin (OR, 1.09; 95% CI, 0.69–1.73).8,9

Pooled Data Analysis: An analysis of individual patient data pooled from the 1,292 patients in the ASK, MAST-I, and MAST-E trials showed that treatment with SK was associated with a significantly increase risk of death at 10 days (relative risk [RR], 1.94; 95% CI, 1.55–2.42; p < 0.001) and 3 months (RR, 1.46; 95% CI, 1.24–1.73; p < 0.001).45 There was no difference between SK-treated and patients for death or dependency at 3 months (RR, 0.99; 95% CI, 0.92–1.06; p = 0.72). Treatment with SK was associated with significantly more hemorrhagic transformations (RR, 1.85; 95% CI, 1.58–2.17; p < 0.001). There was a nonsignificant trend to better outcomes in those patients treated in < 3 h (RR, 0.88; 95% CI, 0.73–1.05).45

The SK trials and subsequent metaanalyses and pooled analyses demonstrate convincingly that there is an increase in early mortality and symptomatic ICH when a dose of 1.5 million U of SK is given during a 6-h window after symptom onset. Patients given a combination of SK and aspirin had the worst outcomes.

Recommendation

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

1.4 Intraarterial Thrombolysis for Acute Ischemic Stroke

Intraarterial Thrombolysis: Intraarterial thrombolytic therapy may be delivered either by regional
infusion or by local infusion directly into the thrombus using supraselective catheters. These approaches have the potential advantages of increased recanalization rates, improving the accuracy of diagnosis, and perhaps enhanced safety because of a reduction in the total dose of drug administered. Disadvantages include the limited availability of facilities and of personnel who are capable of performing intra-arterial therapy and the inherent delays in drug administration related to the logistics of assembling an appropriate team and performing an angiogram.

Metaanalysis Data: The Cochrane metaanalysis of PROACT I and II showed a barely significant reduction in death and disability with intraarterial rpro-UK initiated within 6 h of symptom onset in patients with middle cerebral artery occlusion (OR, 0.55; 95% CI, 0.31–1.00). There was a trend toward increased risk of symptomatic ICH (OR, 2.39; 95% CI, 0.88–8.47) and a weak trend for reduced all-cause mortality associated with the use of rpro-UK.

Individual Trial Results: Two randomized trials comparing intraarterial rpro-UK plus IV heparin vs IV heparin have been conducted in patients with occlusion of the middle cerebral artery (M1 or M2) of < 6 h in duration.46,47 The PROACT I trial treated 40 patients with middle cerebral artery occlusions with either intraarterial rpro-UK (n = 26) or placebo (n = 14).47 All patients received IV heparin. The protocol initially specified a heparin dose of a 100 IU/kg bolus and 1,000 U/h for 4 h. After 16 patients were randomized the heparin dose was reduced to a 2,000 IU/kg bolus and 500 IU/h 4-h infusion on recommendations of the safety committee. The study drug was started a median of 5.5 h after symptom onset. Recanalization rates were significantly higher with rpro-UK (58%) than with placebo (14%; p = 0.017). There was nonsignificant difference in the rate of early symptomatic hemorrhagic transformation, which occurred in 15.4% of the rpro-UK patients and 7.1% of the placebo-treated patients (2p = 0.64). Ninety-day mortality rates (4% in pro-UK group, 7% in the control group) and good clinical outcomes (30.4% vs 21.4%) favored treatment with rpro-UK but did not reach statistical significance. Recanalization rates and the risk of brain hemorrhage were influenced by the dose of heparin.

PROACT II was designed to further test the efficacy and safety of intraarterial rpro-UK in patients with middle cerebral artery occlusion of < 6 h duration.46 A total of 180 patients with angiogram-confirmed middle cerebral artery occlusions were randomized to receive 9 mg of intraarterial rpro-UK plus heparin (n = 121) or heparin alone (n = 59). The heparin dose was the same for both groups (2,000-U bolus and a 500 U/h infusion of heparin for 4 h). A clinically and statistically significant benefit favored rpro-UK in the primary outcome analysis with 40% of treated patients recovering to a mRS of ≤ 2 compared with 25% of control patients (absolute risk reduction, 15%; p = 0.043, relative risk reduction [RRR], 60%). Mortality was 25% in the rpro-UK arm and 27% in the control group. Symptomatic intracranial hemorrhage occurred in 10% of rpro-UK patients and 2% of control patients (p = 0.063). The recanalization rate (TIMI 2 or 3) was 66% for rpro-UK vs 18% for control (p < 0.001). Patients recruited to PROACT II had moderate to severe strokes with a median baseline NIHSS of 17. The median time to start of intraarterial treatment was 5.3 h. Mechanical clot disruption was not permitted. Benefits of rpro-UK were greatest in patients with baseline NIHSS scores of 11–20.

Published Reports of Intraarterial Therapy in Clinical Practice: rpro-UK is not available for routine clinical use. Reports of intraarterial thrombolysis using tPA or urokinase in selected patients have generally reported favorable results, or better than anticipated clinical outcomes, despite increases in the rate of symptomatic ICH.48–56 Treatment times have been beyond 3 h in most cases and patients often had severe stroke syndromes due to large vessel occlusions. Urokinase is not currently available for use in most countries. Some clinicians have utilized radiographic data such as the hyperdense artery sign as selection criteria for intraarterial thrombolysis.57

Basilar Artery Occlusion: The natural history of acute basilar artery occlusion is grim with mortality rates as high as 80 to 90%; the few survivors tend to be severely disabled. Several case series have reported outcomes that appear to be more favorable than expected with intraarterial thrombolysis in patients with acute basilar occlusion.50,58–62 The duration of tissue viability in brainstem ischemia is uncertain and anecdotal reports suggest that brainstem structures may be more resistant to ischemia than cerebral cortex. Exceptional cases of good recovery with treatment as late as 12 h or more have been reported, however, the duration of the therapeutic window in basilar occlusion is uncertain and may be highly variable in individual patients. Decisions to treat must be determined on a case-by-case basis utilizing available clinical and radiologic data and on the availability of the necessary interventional resources. Clearly defined areas of brainstem or cerebellar infarction detected on CT or MRI imaging are unlikely to respond to thrombolysis. When therapy is deemed to be appropriate it should be...
delivered as early as possible. It is unlikely that any large-scale randomized controlled trials of intraarterial therapy will be conducted in patients with basilar occlusion. Many stroke centers offer or proceed with intraarterial thrombolysis for patients with basilar occlusion if the clinician believes there is a reasonable potential for clinically meaningful recovery. Additionally, in light of the poor natural history of acute basilar occlusion many clinicians and interventionalists are reluctant to randomize patients to a placebo-controlled trial.

A systematic analysis of 420 published cases of thrombolytic therapy in acute stroke due to basilar artery thrombosis found no significant difference in death or dependency in patients treated with IV thrombolysis (78%, 59/76) vs intraarterial (76%, 260/344), p = 0.82. A total of 24% and 22% had good outcomes with intraarterial and IV thrombolysis, respectively. Regardless of treatment modality, favorable outcome was strongly associated with recanalization success; 38% of patients with partial or complete recanalization had good outcomes compared to only 2% with no recanalization.

Recommendations

1.4.1. For patients with angiographically demonstrated MCA 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).

Remarks: Intraarterial thrombolytic therapy has not received regulatory approval for acute stroke treatment. Intraarterial therapy requires expertise in stroke management and neuroradiological techniques. Treatment should be limited to clinical trials or to carefully selected patients after informed consent. Intraarterial therapy should be considered only when there are adequate personnel and facilities to ensure appropriate patient selection, and procedural and postprocedural care. Prourokinase is not commercially available, and intraarterial tPA has not been subjected to clinical trials. There is inadequate clinical trial evidence to provide recommendations regarding the optimal thrombolytic agent, dose, or delivery technique. The duration of the therapeutic window for thrombolysis in patients with basilar occlusion is uncertain and is likely highly variable and determined by case-specific variables.

1.5 New and Investigational Therapies

The Interventional Management of Stroke III (IMS III) is expected to enroll 900 subjects comparing the use of combined IV tPA and intraarterial recanalization therapies including tPA and/or intraarterial devices (EKOS catheter or Merci Retriever) to IV tPA alone patients with stroke of < 3 h duration. Desmoteplase, alfimeprase, tenecteplase, and other novel thrombolytic agents are undergoing phase II or phase III studies for acute stroke of up to 9 h duration. These trials use both clinical and neuroimaging criteria for patient selection. These agents have pharmacologic or pharmacokinetic characteristics that may potentially provide for more rapid recanalization and/or reduce the risk of hemorrhagic complications.

Abciximab: Abciximab, a monoclonal antibody directed at the platelet glycoprotein IIb-IIIa receptor, has been evaluated in acute ischemic stroke. The Abciximab Emergent Stroke Treatment Trial (or AbESTT), a phase II study of 400 patients who were randomized to receive abciximab or placebo, showed a nonsignificant trend toward favorable outcomes with abciximab (OR, 1.2; 95% CI, 0.84 to 1.70; p = 0.33). The rate of symptomatic ICH was 3.6% with abciximab therapy compared to 1% with placebo. A phase III study with a planned enrollment of up to 1,800 patients was stopped prematurely by the safety and steering committees due to increased risks of symptomatic ICH and lack of efficacy. The primary cohort consisted of patients who were treated within 5 h of symptom onset. A companion cohort enrolled patients who were treated 5 to 6 h after symptom onset and also a smaller cohort of patients who were treated within 3 h of stroke being present upon awakening. The study was terminated prematurely after 805 patients in all cohorts were enrolled. At 3 months, 33% of patients treated with placebo and 32% of patients treated with abciximab had favorable outcomes based on a dichotomized modified Rankin scale. In the primary cohort, symptomatic or fatal ICH occurred within 5 days in 5.5% of abciximab-treated patients and in 0.5% of placebo-treated patients. At this time, IV abciximab cannot be recommended for use in the treatment of acute ischemic stroke.

Mechanical Devices: Several novel catheter devices designed to expedite clot lysis or extraction are currently available. The Concentric MERCI retriever system has received Food and Drug Administration approval for
clot retrieval in acute ischemic stroke based on the results of the MERCI trial which demonstrated recanalization in 46% (61/159) of patients. In the MERCI trial the overall mortality rate at 90 days was 43.5% and only 22.6% achieved an mRS of ≤ 2. Good neurologic recovery with independence (mRS 0–2) at 90 days was more frequent with successful recanalization compared with unsuccessful recanalization (46% vs 10%, p < 0.0001). Symptomatic ICH (neurologic worsening of ≥ 4 NIHSS points) occurred in 7.8% and clinically significant procedural complications occurred in 7.1%. The MERCI Retriever is an option for patients ineligible for conventional tPA therapy. Clinical and technical expertise is required for the use of the MERCI retriever. More clinical outcome data are required before definitive recommendations can be made regarding the efficacy and safety of this approach.

Ultrasound-Enhanced Thrombolysis: Transcranial Doppler ultrasonography (TCD) has been used to enhance the thrombolytic effect of tPA. In one study 126 patients were randomized to continuous ultrasonography with 2-MHz TCD (n = 63) or placebo (n = 63). Complete recanalization or dramatic clinical response was achieved within 2 h of tPA initiation in 31 patients (49%) of TCD treated patients compared to 19 patients in the control group (30%; p = 0.03). At 3 months, there was a persisting although nonsignificant trend toward favorable outcomes with the use of TCD enhanced thrombolysis (42% vs 29%; p = 0.02). Microbubble-enhanced TCD is undergoing evaluation in efforts to further facilitate tPA reperfusion. Data are presently insufficient to permit recommendations on the use of TCD with or without microbubble enhancement.

1.6 Use of MRI for Patient Selection

The use of MRI rather than CT imaging for selection of patients for thrombolytic therapy is utilized by some stroke centers. However, logistical access issues have limited widespread use and not all stroke patients are able to tolerate MRI imaging. Additionally, attention must be paid to potential time delays as measured by the door-completion of MRI interpretation, rather than just the MRI “table time” in order to ensure that valuable treatment time is not lost. Preliminary data suggest that specific MRI profiles may identify patients who are particularly likely to benefit from thrombolytic therapy. New MRI techniques including perfusion-weighted imaging and diffusion-weighted imaging may detect ischemic injury in the first hour and may reveal the extent of reversible and irreversible injury. In addition, MRI appears to be highly sensitive for identification of acute brain hemorrhage. In the DEFUSE study, a baseline MRI scan with diffusion-weighted imaging and perfusion-weighted imaging was obtained immediately prior to administration of IV tPA in 74 consecutive stroke patients treated 3 to 6 h after symptom onset. The results of this study demonstrated that baseline MRI findings can differentiate subgroups that are likely to benefit from reperfusion therapies, from those who are unlikely to benefit, or may be harmed. Early reperfusion was significantly associated with an increased odds of achieving a favorable clinical response in patients with a perfusion/diffusion mismatch (OR, 5.4; p = 0.039) Patients with a no-mismatch MRI profile did not appear to benefit. Several randomized trials, in which patient selection is based on MRI criteria, are currently in progress and further data are required to validate this approach before recommendations can be made.

2.0 Acute Ischemic Stroke: Patients Not Eligible for Thrombolysis

For acute cerebral infarction patients who are not eligible for IV or intraarterial thrombolysis therapy, clinicians can consider a variety of antithrombotic agents. Clinical trials have evaluated several anticoagulants (heparin, low molecular weight heparins, and heparinoids) and aspirin. Other antiplatelet agents proven effective in the long-term reduction of recurrent ischemic events are undergoing evaluation in the acute setting. The rationale for the use of antithrombotic therapy for treatment of acute ischemic stroke is based on two premises: (1) reduction of the risk of stroke progression or recurrent cerebral thromboembolism; and (2) prevention of venous thromboembolic complications such as deep venous thrombosis (DVT) and pulmonary embolism (PE). The use of antithrombotic agents is complicated by the existence of different stroke etiologic subtypes, each of which imparts a differential risk of these outcomes. The therapeutic approach to the acute stroke patient should consider these distinct pathophysiologic mechanisms. Unfortunately, there are often ambiguities in the clinical evaluation that lead to uncertainty regarding the stroke mechanism. In the early hours of presentation with an acute stroke, the mechanism of the infarction is frequently not clear and decisions regarding therapy are based on presumptive diagnostic subtypes. Few acute stroke clinical trials, therefore, have been adequately designed to accurately assess the differential efficacy of antithrombotic therapies by stroke subtype.
Subtypes of Ischemic Stroke

Strokes caused by extracranial or intracranial large artery atherosclerosis appear to have the greatest risk of worsening and recurrence in the early period after hospitalization. In the NINDS Stroke Data Bank, the atherosclerotic stroke subgroup had a 30% risk of worsening during the acute hospitalization and a 7.9% risk of stroke recurrence within 30 days. In the North American Symptomatic Carotid Endarterectomy Trial (NASCET), medically treated patients with transient ischemic attack (TIA) or stroke and ipsilateral carotid stenosis > 70% had a 26% risk of ipsilateral stroke at 2 years. Data from the Northern Manhattan Stroke Study indicated that the 30-day risk of recurrence was 8% for patients with extracranial atherosclerosis and 7.1% for those with intracranial atherosclerosis. These risks were nearly sixfold greater than those for nonatherosclerotic stroke. Moreover, recurrent stroke risks from natural history studies are generally greater than those observed in the control groups of recent randomized trials which reported risks of 0.6 to 2.2% per week. Data from the Warfarin Aspirin Symptomatic Intracranial Disease trial have also documented a 25% 2-year risk of stroke among symptomatic patients with > 70% stenosis of an intracranial artery.

Causes of worsening and recurrence in patients with large artery atherosclerotic stroke include propagation or progression of the thrombosis, distal embolism, or failure of collateral vessels to compensate for the reduced cerebral perfusion. For these reasons, anticoagulation has been advocated as a rational approach for these patients on the basis of theoretical pathophysiologic considerations despite the absence of supportive clinical trial evidence.

Progressing Stroke: Also referred to as stroke in evolution, progressing stroke has frequently been considered an indication for anticoagulation, although supportive randomized clinical trial data are scant. Studies performed in the 1950s and 1960s suggested that IV heparin therapy may be beneficial for patients with unstable ischemic stroke with as much as a 50% reduction in the likelihood of further worsening. These studies, however, were either not randomized or blinded, had poorly defined inclusion and exclusion criteria, or did not use standardized assessments for outcomes. Other nonrandomized studies of consecutive patients with unstable stroke who received IV heparin have shown high rates (27 to 50%) of further progression despite treatment.

Cardioembolic Strokes: Older studies suggested a recurrence risk that approached 1%/d in the first 14 days; however, more current studies have found the risk of early recurrence to be considerably lower. The cause of an early recurrence in patients with cardioembolic stroke is usually another thrombus becoming dislodged from the intracardiac source, and the risk of early stroke recurrence is likely related to the underlying cardiac lesion. For example, one study found a high rate of early recurrence in a large group of cardioembolic stroke patients who had rheumatic heart disease, prosthetic valves, or documented intracardiac thrombi, but a significantly lower recurrence rate in atrial fibrillation patients. Strokes related to atrial fibrillation, however, are often major and associated with significant disability.

Small Artery Occlusions: Infarcts caused by small artery occlusions (lacunar strokes) have the lowest early recurrence risk and the best survival rates, but still cause significant functional morbidity. Worsening or evolution of the infarct can occur, although motor deficits improve to a greater extent in strokes due to small artery occlusions compared to nonlacunar stroke syndromes. The underlying mechanism in the majority of lacunar strokes arises from small vessel disease, usually caused by lipohyalinosis. Thrombosis, as well as platelet-fibrin complexes, can lead to occlusion after the small-vessel lumen has been significantly narrowed. Large-vessel atherosclerosis and embolism can also lead to small vessel occlusions, but these mechanisms probably occur in < 25% of patients with lacunar syndromes.

Some strokes are difficult to reliably classify into these categories and have been labeled cryptogenic infarcts. These patients typically have no carotid bruit or TIA ipsilateral to the hemisphere affected by the stroke and no obvious history suggestive of cardiac embolism, and usually do not present with a lacunar syndrome. The CT or MRI scan performed may be normal, show an infarct limited to a surface branch territory, or show a large zone of infarction affecting regions larger than can be accounted for by a single penetrant arterial territory. Noninvasive vascular imaging fails to demonstrate an underlying large vessel occlusion or stenosis. No cardiac source of embolism is uncovered by echocardiography, ECG, or Holter monitoring.

For those infarcts considered cryptogenic, theoretical considerations favor the diagnosis of an embolism despite the absence of a definitive source. Emerging technologies have led to the suggestions that some cryptogenic infarcts may be explained by hematologic disorders causing hypercoagulable states, paradoxical emboli through a patent foramen ovale (PFO), unrecognized arterial lesions (dissections, mild atherosclerosis), or aortic arch atherosclerosis.
acute treatment of cryptogenic stroke should differ from that of other ischemic stroke subtypes.

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

Metaanalysis: A large metaanalysis of 22 trials among 23,547 patients showed that immediate anticoagulation of patients with acute ischemic stroke was not associated with a significant reduction in death or dependency.102 Although anticoagulants were associated with about 9 fewer recurrent ischemic strokes per 1,000 treated, this was offset by a similar increase of 9 symptomatic intracranial hemorrhages per 1,000 treated.

Individual Trials: Randomized trials using unfractionated heparin (UFH), low-molecular-weight heparins, and heparinoids have helped clarify the benefits and risks of anticoagulants for treatment of acute ischemic stroke. These trials have been primarily aimed at altering outcomes such as early recurrence, worsening, mortality, and functional disability. Various doses and routes of administration have been used ranging from subcutaneous (SC) fixed doses to adjusted doses of these agents.

Despite the clinical use of full-dose IV UFH, to our knowledge, only a single randomized trial has evaluated this regimen compared with placebo for patients with acute stable stroke since 1980. No significant difference in stroke progression or neurologic outcome was detected in this relatively small study (n = 225).103 This trial had a broad treatment window of 48 h from stroke onset and excluded patients with progressing stroke. In addition, because of the small sample size, the study had adequate power to detect only a relatively large difference in efficacy between heparin and placebo. The Rapid Anticoagulation Prevents Ischemic Damage (RAPID) randomized trial was designed to compare weight-adjusted continuous IV UFH to aspirin among nonlacunar ischemic stroke patients treated within 12 h of onset. Although 1,184 patients were planned, the trial was terminated 30 months later due to poor recruitment after only 67 patients were randomized. Sample sizes were insufficient to reach any meaningful conclusions.104

SC administration of heparin was evaluated in the International Stroke Trial (IST).105 In this unblinded megatrial, 19,435 patients with suspected acute ischemic stroke from 467 hospitals in 36 countries were randomized within 48 h of onset (median, 19 h) to aspirin, SC heparin, both, or neither in a factorial design. Half were allocated 300 mg aspirin and half “avoid aspirin”; half were allocated UFH, administered SC, in two different doses (5,000 U bid or 12,500 U bid) and the remaining half “avoid heparin.” In this study, therapy could be started before a CT scan was obtained to verify that the stroke was not hemorrhagic (this occurred in one third of the cases), and the level of anticoagulation achieved was not monitored. The patients were followed by the local investigators until discharge or for 14 days, whichever was sooner, and at 6 months by telephone or postal questionnaire by each national coordinating center. The primary outcomes were death within 14 days and death or dependency at 6 months. Secondary outcomes included recurrent ischemic stroke, hemorrhagic stroke, PE, or transfused or fatal extracranial hemorrhage within 14 days.

IST data were analyzed with the two heparin groups combined. There was no significant difference in 14-day mortality (heparin, 9.0% vs no heparin, 9.3%) or 6-month outcome (heparin, 62.9% dead or dependent vs no heparin, 62.9%). Even among the 843 patients treated within 3 h and 2,322 patients treated within 4 to 6 h, there was no benefit for heparin at 6 months. At 14 days, recurrent ischemic strokes were significantly reduced in the heparin groups (from 3.8 to 2.9%) but hemorrhagic stroke was significantly increased (from 0.4 to 1.2%), yielding no net benefit. In the subgroup of patients who presented with atrial fibrillation and acute ischemic stroke, heparin significantly reduced the risk of 14-day ischemic stroke recurrence from 4.9 to 2.8%, but an increased risk of hemorrhagic stroke (2.1 vs 0.4%) neutralized the potential benefits. Blood transfusion or fatal extracranial hemorrhages were significantly more frequent among those allocated to heparin. The higher-dose regimen (12,500 U bid) was associated with more systemic bleeding, hemorrhagic strokes, and a significantly increased risk of death or nonfatal stroke at 14 days. The low-dose heparin regimen (5,000 U bid) significantly reduced the risk of early death or nonfatal stroke, with only a slight and nonsignificant excess of bleeding side effects. Patients who received both low-dose heparin and aspirin had the lowest rate of stroke recurrence, or PE, and no significant increase in bleeding risk (compared with patients who received low-dose heparin without aspirin). In summary, the heparin data from IST suggest that the use of early unmonitored SC heparin will reduce early stroke recurrence risks, but these benefits can be eliminated by increased hemorrhagic complications. The use of lower doses of heparin may provide more benefits than hemorrhagic side effects.

Low-molecular-weight-heparin fragments have a higher anti-factor Xa to anti-factor IIa ratio effect than standard heparin, therefore a potentially greater antithrombotic effect. They cause less inactivation of
thrombin, less inhibition of platelets, and less vascular permeability, which may reduce bleeding risk. The low-molecular-weight heparin nadroparin (fraxiparin) was tested in the setting of acute ischemic stroke with mixed results. In the Hong Kong trial, the nadroparin-treated patients had better 6-month outcomes.\textsuperscript{106} In this trial, 308 patients were randomized to three groups (high- or low-dose nadroparin and a placebo group) and treated within 48 h (mean of 27 h) of stroke onset for 10 days. Although no significant effect was noted in 3-month outcomes, there was a significant dose-dependent effect on the risk of death or dependency at 6 months. Using a very similar design, a larger multicenter trial completed in Europe, Canada, and Australia (the Fraxiparine in Ischemic Stroke Study (FISS bis Study)) was unable to corroborate these beneficial effects. In this trial 767 acute ischemic stroke patients were enrolled within 24 h into two dose groups and placebo. The 6-month risk of death or dependency was 59.2\% for the high-dose, 57.2\% for the low-dose, and 56.8\% for the placebo groups.\textsuperscript{107}

The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) evaluated the low-molecular-weight heparinoid danaparoid (ORG 10172) among 1,281 patients with ischemic stroke treated within 24 h of onset.\textsuperscript{106} In this multicenter, blinded, placebo-controlled trial, patients were treated for 7 days with an IV infusion of the heparinoid, and daily dose adjustments were based on antifactor Xa units. To our knowledge, this was the only heparinoid trial to include a bolus dose and make dose adjustments. The mean time between symptom onset and treatment was 15.5 h. Neurologic deficits were evaluated daily using the NIHSS. The primary outcome was based on the 3-month assessment of the GOS and the BI with a favorable status defined as GOS of 1 or 2 and BI of 60 or more. Overall, there was no significant difference in the proportion of patients with favorable outcomes at 3 months in the danaparoid group compared with the placebo group (75.2\% vs 73.7\%). Favorable outcomes at 7 days were slightly increased in the danaparoid group compared with the placebo group (59.2\% vs 54.3\%; \( p = 0.07 \)) while the number of patients with very favorable outcomes was significantly higher in the danaparoid group (33.9\% vs 27.8\%; \( p = 0.01 \)). There was no significant reduction in stroke progression, 7-day mortality, or the risk of stroke recurrence or systemic embolic events. In a predefined subgroup analysis from TOAST, patients with large-artery atherosclerotic stroke revealed a benefit in favorable outcome from danaparoid at 3 months (69.1\% vs 54.7\%; \( p = 0.04 \)). This subgroup analysis offers some evidence in favor of the efficacy of heparinoids for treatment of acute large-artery atherosclerotic stroke.\textsuperscript{108}

In a recently published trial, 353 Asian stroke patients with confirmed large artery occlusive disease were randomized to either SC nadroparin (3,800 anti-factor Xa IU/0.4 mL) bid or aspirin 160 mg/d within 48 h of stroke onset and continued for 10 days. The proportion of patients with good outcomes at 6 months (BI \( \geq 85 \)) was not different between the groups.\textsuperscript{109}

Other studies using different low-molecular-weight heparin agents with fixed SC doses have also been completed. Tinzaparin was evaluated in a blinded, randomized, aspirin-controlled trial of patients with acute ischemic stroke treated within 48 h.\textsuperscript{110} Among 1,486 randomized patients, the primary outcome of independence at 6 months was similar in the high-dose tinzaparin group (41.5\%), medium-dose group (42.4\%), and aspirin group (42.5\%). There was no difference in recurrent stroke or any of the baseline stroke subgroups including the cardioembolic subgroup. DVT was significantly reduced in the high-dose group, while symptomatic ICH was increased. Another study compared four different doses of a low-molecular-weight heparin (certoparin) among ischemic stroke patients treated within 12 h of onset.\textsuperscript{111} No dose-dependent difference was observed in efficacy and bleeding was greater in the higher-dose group.

**Cardioembolic Stroke:** Oral anticoagulants substantially reduce the long-term risk of cardiac embolism, but the evidence supporting the use of anticoagulation in patients with acute cardioembolic stroke is based on limited data from case series and a single small open randomized clinical trial.\textsuperscript{112-114} This randomized trial was terminated early after only 45 patients were enrolled. No early recurrence occurred in the group who received anticoagulants, compared with a 10\% recurrence rate (two of 20) in the patients who did not receive anticoagulants.

The use of heparin for acute cardioembolic stroke has been challenged by the lack of efficacy of both unfractionated SC heparin in the subgroup with atrial fibrillation in IST, and heparinoid in the cardioembolic subgroup in the TOAST trial. Low molecular-weight heparin was evaluated in the Heparin in Acute Embolic Stroke Trial (HAEST).\textsuperscript{91} In this study 449 patients with atrial fibrillation and acute ischemic stroke (within 30 h after onset) were randomized to treatment with aspirin (160 mg/d) vs a high dose of the low-molecular-weight heparin, dalteparin (100 IU/kg SC bid). The frequency of recurrent ischemic stroke within the first 14 days was 8.5\% in the dalteparin group and 7.5\% in the aspirin
group. No differences in these primary outcomes or multiple secondary outcomes were detected. The frequency of recurrence, progression, death, or symptomatic cerebral hemorrhage within 14 days was greater in the dalteparin group compared to the aspirin group (24.6% vs 16.9%, p = 0.048); the risk for extracerebral hemorrhages was also greater in the dalteparin group (5.8% vs 1.8%, p = 0.028). It should be noted that physicians had the option to enroll patients in this trial based on their clinical judgment regarding the benefits of anticoagulation and some patients with atrial fibrillation associated with high risk features may not have been randomized.

Limitations of Available Data: Most reviews have strongly discouraged the indiscriminate use of heparin and low-molecular-weight heparins for acute ischemic stroke. The risk of symptomatic hemorrhagic transformation in these acute anticoagulation trials is less than that observed with thrombolysis, but greater than the risk with antiplatelet therapy. A large infarct size, judged by neuroimaging findings or the clinical syndrome, and elevated BP's are predictors of a greater risk of hemorrhagic transformation. The risk is also greater among those treated with larger doses of anticoagulation.

Some limitations of clinical trials of anticoagulants for stroke treatment include a longer treatment delay than in recent thrombolytic therapy trials, the inability to accurately identify etiologic stroke mechanisms at stroke onset, the lack of serial neurologic assessments to evaluate worsening, the high likelihood that patients with progressing strokes (stroke in evolution) or at high cardioembolic risk were excluded from these trials, the large percentage of stroke patients with mild deficits, and insufficient sample sizes to adequately evaluate individual stroke subtypes. Moreover, recent trials have documented a much lower risk of early recurrence than originally anticipated leading to the requirement of much larger sample sizes to adequately evaluate efficacy as a primary end point. Questions remain regarding the efficacy of heparin for treatment of progressing stroke, the role of immediate anticoagulation for large artery atherosclerotic stroke, and the risk-benefit ratio for acute cardioembolic stroke.

Recommendation

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. Clinical trials have not, however, adequately evaluated adjusted dose IV anticoagulation in these selected stroke patients. To our knowledge, no adequately powered trials have evaluated the role of very early anticoagulation (< 12 h after stroke onset) in any stroke population. The risk of hemorrhage may outweigh any benefits.

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

Metaanalysis: A metaanalysis from 41,399 subjects enrolled in nine trials evaluated the efficacy of antiplatelet agents. The two trials contributed 98% of the data. Death or dependency at 6 months was significantly less for those treated with aspirin (OR, 0.94; 95% CI, 0.91–0.98). For every 1,000 acute strokes treated with aspirin, 10 patients made a complete recovery at 6 months, about 7 fewer early recurrent ischemic strokes were observed and 1 less PE at the expense of two or more symptomatic intracranial hemorrhages. These overall small, but significant, absolute benefits and low cost of aspirin represent important public health measures to improve stroke outcomes despite the small increase in hemorrhage risk.

Individual Trials: Aspirin is the only antiplatelet agent that has been evaluated for the treatment of acute ischemic stroke. Other antiplatelet agents such as ticlopidine, clopidogrel, or extended-release dipyridamole plus aspirin have not been evaluated in the setting of acute ischemic stroke; however, some ongoing trials are testing the efficacy of loading doses of clopidogrel and aspirin after acute TIA or ischemic stroke. Data on aspirin are available from two mega-trials, IST and the Chinese Acute Stroke Trial (CAST). These studies both found that the use of early aspirin in patients treated within 48 h of stroke onset (median time to randomization was 19 h in IST, and the mean time to randomization was 25 h in CAST) reduced both stroke recurrence risk and mortality. Among 19,435 patients randomized in IST, aspirin-allocated patients had slightly fewer deaths within 14 days (9.0% vs 9.4%), significantly fewer recurrent ischemic strokes (2.8% vs 3.9%), no excess of hemorrhagic strokes (0.9% vs 0.8%), and a trend toward a reduction in death or dependence at 6 months (61.2% vs 63.5%).

In CAST, 21,106 patients with acute ischemic stroke within 48 h of onset were randomized to receive 160 mg/d of aspirin or a placebo for up to 4
weeks. The primary end points were death from any cause at 4 weeks and death or dependence at discharge. The majority of patients (87%) had a CT scan before randomization. There were small but significant reductions in the aspirin group in both early mortality (3.3% vs 3.9%; p = 0.04) and recurrent ischemic strokes (1.6% vs 2.1%; p = 0.01). At discharge, there was a smaller proportion of patients who were dead or dependent in the aspirin-treated group (30.5% vs 31.6%; p = 0.08). In combination, the IST and CAST trials demonstrate that the use of aspirin in the treatment of acute ischemic stroke is safe and produces a small but definite net benefit.

Another smaller trial of 441 patients who were not on any antplatelets at the time of an ischemic stroke and were randomized to 325 mg aspirin vs placebo failed to detect any difference in the primary outcome of stroke progression by discharge. Stroke progression occurred in 15.9% of the aspirin group and 16.7% of the placebo treated. Three-month outcomes were similar in the two groups.

Recommendation

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

Remarks: Aspirin should be started within 48 h of stroke onset and may be used safely in combination with low doses of SC heparin for DVT prophylaxis. Aspirin is contraindicated among those with aspirin allergy or those with active GI bleeding. Following the initial dose, reducing the does to 50 to 100 mg/d may reduce bleeding complications.

2.3 Antithrombotic Therapy for Prevention of DVT and PE in Acute Ischemic Stroke

DVT and PE are frequent complications of stroke, with about 5% of early deaths attributed to PE. Large trials performed in other high-risk groups (such as patients who underwent major surgery) indicate that heparin can reduce the risk of DVT and PE by about 60%. For acute stroke patients, few randomized trials have individually been able to demonstrate a significant decrement in the risk of these complications. In an overview analysis among acute stroke patients, anticoagulants were associated with 4 fewer pulmonary emboli per 1,000 (OR, 0.60; 95% CI, 0.44–0.81). In the IST, there was a significant reduction in the frequency of fatal or nonfatal PE, from 0.8 to 0.5%, among those treated with SC UFH (p < 0.05). Aspirin therapy was not effective for preventing PE in this study.

Low-molecular-weight heparins have been found to be equivalent to or better than UFH in preventing DVT. In a metaanalysis among 740 acute ischemic stroke subjects from four trials, there was a significant reduction in the odds of DVT (OR, 0.52; 95% CI, 0.56–0.79) among those allocated to low-molecular-weight heparins or heparinoids vs standard UFH. There were too few major events such as PE, death, or major hemorrhage, however, to make meaningful comparisons (see article on “Prevention of Venous Thromboembolism”). Two trials of direct comparisons between a low-molecular-weight heparin and UFH have shown similar safety and efficacy for enoxaparin and noninferiority for certoparin.

The PREVAIL (Prevention of Venous thromboembolism after Acute Ischemic stroke) trial was an open-label, randomized comparison of either enoxaparin 40 mg SC qd or UFH at 5,000 U SC q12h in patients with ischemic stroke; 1,762 patients were randomized within 48 h of symptom onset and were stratified on stroke severity (NIHSS < or ≥ 14). The primary efficacy end point was the combination of symptomatic or asymptomatic DVT, symptomatic PE, or fatal PE among patients who received one or more dose and had a laboratory assessment for venous thromboembolism or a clinical event (the “efficacy population”). After a mean of 10.5 days of treatment, 10% of patients randomized in the enoxaparin group had a primary end point compared to 18% in patients randomized to UFH, yielding a 43% RRR (0.57; 95% CI, 0.44–0.76; p = 0.0001). DVT was primarily diagnosed on the basis of a bilateral contrast venography at the end of treatment period; ultrasonography was performed if venography was not possible. The vast majority of the end points in each group were asymptomatic DVTs. The results for proximal DVT were 5% in the enoxaparin group and 10% in the UFH group (p = 0.0003). Any bleeding occurred with the same frequency (8%) in both treatment groups. The risk of both symptomatic intracranial bleeding and major extracranial hemorrhage was also similar in both groups (1% each), but there were more major extracranial bleedings in the enoxaparin group (p = 0.015). These results were similar in both severity groups. Although the reduction in asymptomatic DVT was substantial with enoxaparin, the absolute increase in major extracranial bleeding was similar to the reduction in symptomatic DVT/PE.

DVT and PE prophylaxis are essential reasons to consider early low-dose anticoagulant therapy in acute stroke patients. For patients with contraindications to anticoagulants, intermittent pneumatic compression (IPC) devices or elastic stockings are recommended (see article on “Prevention of Venous Thromboembolism”).
Recommendations

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

Remarks: Low-dose heparin should be restricted for 24 h after administration of thrombolytic therapy. Low-dose heparin may be used safely in combination with aspirin.

2.3.2. For patients who have contraindications to anticoagulants, we recommend that clinicians use IPC devices or elastic stockings (Grade 1B).

3.0 DVT/PE Prophylaxis in Patients With Intracerebral Hemorrhage

3.1 IPC for DVT/PE Prophylaxis in Patients With Intracerebral Hemorrhage

One study has addressed the benefits of IPC in the prevention of venous thromboembolism during the first 10 days after intracerebral hemorrhage (ICH)130; 151 patients were randomized to receive elastic stockings alone or combined with IPC. IPC significantly decreased the occurrence of asymptomatic DVT (15.9% in the elastic stockings alone group, compared with 4.7% in the IPC group). Symptomatic DVT or PE was not documented in either group.

Recommendation

3.1. In patients with an acute ICH, we recommend the initial use of IPC devices (Grade 1B).

3.2 Heparin for DVT/PE Prophylaxis in Patients With ICH

To our knowledge, only one small study is available to address the risk of early prophylactic therapy with anticoagulants in patients with ICH.131 In this study, 22 patients with spontaneous ICH were randomized to receive elastic stockings alone or combined with IPC. IPC significantly decreased the occurrence of asymptomatic DVT (15.9% in the elastic stockings alone group, compared with 4.7% in the IPC group). Symptomatic DVT or PE was not documented in either group.

Recommendation

3.2. In stable patients, we suggest low-dose SC heparin as soon as the second day after the onset of the hemorrhage (Grade 2C).

Underlying values and preferences: Given the uncertainty about the risk of heparin in this setting, this recommendation places a relatively high value on reducing the consequences of thromboembolism and a relatively lower value on minimizing the risk of cerebral rebleeding.

4.0 Stroke Prevention

The Antithrombotic Trialists’ Metaanalysis

Platelet antiaggregation drugs prevent strokes. Aspirin is the most widely studied antiplatelet drug and most broadly used for this purpose. Clinical trial results in the 1980s with ticlopidine and 1990s with clopidogrel showed they are also effective for prevention of stroke and other vascular events in patients with cerebrovascular disease and they were approved in 1991 and 1997, respectively, in the United States. Dipyridamole (particularly when combined with aspirin) also is effective for prevention of stroke and the combination was approved for this indication in 1999 in the United States. The selection of individual drugs is primarily based on interpretation of their relative efficacy, safety, and cost.

The Antiplatelet Trialists123 conducted a metaanalysis that assessed the effect of antiplatelet drugs in patients with various manifestations of atherosclerosis. An update of their metaanalysis was published in 2002 and included studies published prior to September 1997.132 The Trialists also changed their name to the Antithrombotic Trialists. This latest analysis132 included 144,051 patients with previous myocardial infarction, acute myocardial infarction, previous TIA/stroke, and acute stroke, as well as other patients at increased risk of atherothrombotic events. The Antithrombotic Trialists emphasize the composite outcome of stroke, myocardial infarction, or vascular death. This outcome cluster includes hemorrhagic stroke and death due to hemorrhage. They also analyzed nonfatal stroke, nonfatal myocardial infarction, vascular death, and death from any cause independently. They express the treatment effects for the various vascular outcomes as odds reductions.

The Antithrombotic Trialists found that overall (in all kinds of patients at high risk for vascular outcomes), antiplatelet drugs reduce the odds of the composite outcome of stroke, myocardial infarction, or vascular death in secondary prevention by about 25%. The odds reduction attributable to aspirin alone was 23%. They found that antiplatelet drugs reduce the odds of a nonfatal stroke by 25%, nonfatal myocardial infarction by about 34%, and vascular mortality by 15%.
The Antithrombotic Trialists also analyzed the differences in the response of patients over and under the age of 65 years, and by sex. While some variation is seen, all groups—young and old, men and women—benefit to a similar proportionate degree from antiplatelet therapy. The same is true for patients with hypertension compared with those without hypertension, and diabetes compared with no diabetes.

An important issue arising from the Antithrombotic Trialists' analyses is whether the effect of various antiplatelet drugs on prevention of strokes, myocardial infarctions and vascular deaths is the same in patients entering studies because of prior stroke/TIA as it is for patients entering because of prior myocardial infarction or other vascular disorders. The Antithrombotic Trialists found that whereas all antiplatelet drugs reduced the odds of stroke, myocardial infarction, or vascular death in all high-risk patients by 25%, the odds reduction in patients with prior stroke/TIA was 22%. Additionally, Algra and van Gijn performed a mini-metaanalysis showing that in the 10 trials that evaluated the benefit of aspirin alone in patients who had prior stroke or TIA, aspirin reduced the odds for the cluster of stroke, myocardial infarction, or vascular death by only 16%. When this odds reduction is converted to the more conventional RRR, the benefit over placebo is only 13%.

Differences in antiplatelet effects in different populations of patients may occur because the etiologic mechanisms for stroke may differ, or stroke patients may have a higher rate of recurrent strokes, which may be more difficult to prevent than myocardial infarctions. For this review, we will focus on patients with prior stroke or TIA, and for outcome events we will emphasize stroke alone, and the cluster of stroke, myocardial infarction, or vascular death. The focus on stroke as an outcome is important because patients who experience a stroke or TIA are most likely to have a stroke as their next serious vascular outcome. The focus on the composite cluster also is important because stroke and TIA patients often die of myocardial infarction or other vascular causes as well recurrent stroke. Table 3 summarizes the results of randomized trials of studies of antiplatelet agents for secondary prevention of noncardioembolic stroke.

4.1 Prevention of Cerebral Ischemic Events in Patients With Noncardioembolic TIA or Stroke: Antiplatelet Drugs vs Placebo or vs an Alternative Antiplatelet Drug

Aspirin: The Swedish Aspirin Low-Dose Trial compared aspirin, 75 mg/d, with placebo in 1,360 patients with minor stroke/TIA. The 18% RRR in stroke plus all death in the aspirin-treated group was statistically significant (p = 0.02). The RRR in stroke, myocardial infarction, or vascular death was 17%, and was also statistically significant. This degree of risk reduction is comparable to the 13% that Algra and van Gijn found for all doses of aspirin in similar patients.

The Dutch TIA Trial compared two dosage regimens of aspirin, 30 mg/d vs 273 mg/d, in 3,131 patients with minor stroke/TIA. The primary outcome measure was stroke, myocardial infarction, or vascular death. The investigators found that 30 mg of aspirin daily was no less effective than 273 mg, and there were fewer bleeding events on the lower dose. These latter two trials, along with the earlier UK-TIA Trial and the Algra and van Gijn meta-analysis, led many clinicians to believe there are no important differences in daily doses of aspirin between 30 mg and 1,300 mg for preventing stroke and other vascular events. However, low-dose aspirin is less gastrotoxic. In 1996, the European Stroke Prevention Study-2 (see below) reported that 50 mg/d of aspirin given to patients following stroke or TIA reduced the risk of stroke, and stroke or death, by 18% and 13%, respectively. In 1998, the US Food and Drug Administration published their new recommendation that 50 to 325 mg of aspirin daily be used for prevention of ischemic stroke. One additional direct comparison of low and high aspirin doses was studied in patients undergoing carotid endarterectomy (the ASA and Carotid Endarterectomy [ACE] trial). ACE compared, head-to-head, aspirin at low doses (81 or 325 mg/d) vs high doses (650 or 1,300 mg/d) in 2,804 patients treated for a total of 3 months. There were no significant differences between low and high doses for any end point at 30 days, or for the end points stroke and death, and ipsilateral stroke and death at 3 months. Patients who received low-dose aspirin had a significantly lower rate of stroke, myocardial infarction, and death at 3 months (p = 0.03). The ACE results lend further direct support to the premise that low-dose aspirin is at least as effective as high-dose aspirin.

Ticlopidine: Ticlopidine hydrochloride is a thienopyridine. It blocks the adenosine diphosphate (ADP) P2Y12 receptor and inhibits ADP-induced fibrinogen binding to platelets, a necessary step in the platelet aggregation process. It has been shown to be effective for the prevention of vascular outcomes in several randomized studies. Two large trials assessed ticlopidine for the prevention of stroke and other vascular events in patients presenting with cerebrovascular symptoms. The Ticlopidine Aspirin Stroke Study (TASS) enrolled 3,069 patients who presented within 3 months...
<table>
<thead>
<tr>
<th>Author/yr</th>
<th>Interventions</th>
<th>Patients Analyzed, No./Total</th>
<th>Length of Follow-up</th>
<th>Major Bleeding, No./Total (95% CI)</th>
<th>Total Mortality, No./Total (95% CI)</th>
<th>Composite Primary Outcome, No./Total (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dutch TIA Trial Study Group</td>
<td>Aspirin 283 mg; Aspirin 30 mg</td>
<td>Aspirin 283 mg: 1,576/1,576; Aspirin 30 mg: 1,555/1,555</td>
<td>52 mo</td>
<td>Aspirin 283 mg: 53/1,576 (3.4%); Aspirin 30 mg: 40/1,555 (2.6%) RR: 1.31 (0.87, 1.90)</td>
<td>Aspirin 283 mg: 1,576 (15.2%); Aspirin 30 mg: 1,555 (14.7%) RR: 1.04 (0.88, 1.23)</td>
<td>Aspirin 283 mg: 240/1,576 (15.2%); Aspirin 30 mg: 228/1,555 (14.7%) RR: 1.04 (0.88, 1.23)</td>
<td>Nonfatal episodes of bleeding were considered major if a hospital visit and treatment were necessary</td>
</tr>
<tr>
<td>UK-TIA Study Group</td>
<td>Aspirin 1,200 mg/d; Aspirin 300 mg/d</td>
<td>Aspirin 1,200 mg: 815/815; Aspirin 300 mg: 806/806</td>
<td>7 yr</td>
<td>Aspirin 1,200 mg: 112/815 (13.7%); Aspirin 300 mg: 109/806 (13.5%) RR: 1.02 (0.80, 1.30)</td>
<td>Aspirin 1,200 mg: 162/815 (19.9%); Aspirin 300 mg: 162/806 (20.1%) RR: 0.99 (0.81, 1.20)</td>
<td>Aspirin 1,200 mg: 201/815 (24.8%); Aspirin 300 mg: 201/806 (25.0%) RR: 0.99 (0.88, 1.12)</td>
<td></td>
</tr>
<tr>
<td>Diener et al</td>
<td>Clopidogrel 75 mg/d; Aspirin 75 mg/d</td>
<td>C-A: 3,797/3,797; Clopidogrel: 3,802/3,802</td>
<td>18 mo</td>
<td>C-A: 73/3,759 (1.9%); Clopidogrel: 22/3,802 (0.6%) RR: 3.34 (2.08, 5.36)</td>
<td>C-A: 201/3,797 (5.3%); Clopidogrel: 201/3802 (5.3%) RR: 1.00 (0.83, 1.21)</td>
<td>C-A: 596/3,797 (15.7%); Clopidogrel: 636/3802 (16.7%) RR: 0.94 (0.85, 1.04)</td>
<td>Major bleeding: fatal bleeding and primary intracranial hemorrhage, or bleeding that caused hemodynamic compromise requiring blood or fluid replacement, ionotropic support, or surgical intervention (GUSTO IV definition)</td>
</tr>
<tr>
<td>Bhatt et al</td>
<td>Clopidogrel 75 mg/d; Aspirin 325 mg/d</td>
<td>C-A: 7,802/7,802; Aspirin: 7,801/7,801</td>
<td>18 mo</td>
<td>C-A: 130/7,802 (1.7%); Aspirin: 104/7,801 (1.3%) RR: 1.25 (0.97, 1.61)</td>
<td>C-A: 371/7,802 (4.8%); Aspirin: 374/7,801 (4.8%) RR: 0.99 (0.86, 1.14)</td>
<td>C-A: 534/7,802 (6.8%); Aspirin: 573/7,801 (7.3%) RR: 0.93 (0.83, 1.05)</td>
<td></td>
</tr>
<tr>
<td>Diener et al</td>
<td>Clopidogrel 75 mg/d; Aspirin 50 mg/d</td>
<td>D-A: 1,650/1,650; Dipyridamole: 1,654/1,654</td>
<td>2 yr</td>
<td>D-A: 185/1650 (11.2%); Dipyridamole: 187/1654 (11.4%) RR: 0.99 (0.81, 1.19)</td>
<td>D-A: 206/1650 (12.5%); Dipyridamole: 211/1654 (12.4%) RR: 0.76 (0.64, 0.90)</td>
<td>D-A: 182/1650 (11.2%); Dipyridamole: 182/1654 (11.4%) RR: 0.99 (0.81, 1.19)</td>
<td>ESPS2 Major bleeding: significantly disabling with persistent sequel; intraocular bleed led to significant loss of vision; or transfusion of ≥ 3 U of RBCs or equivalent whole blood</td>
</tr>
<tr>
<td>American-Canadian Co-operative Study Group</td>
<td>Aspirin 283 mg; Aspirin 30 mg</td>
<td>Aspirin 283 mg: 1,576/1,576; Aspirin 30 mg: 1,555/1,555</td>
<td>52 mo</td>
<td>Aspirin 283 mg: 53/1,576 (3.4%); Aspirin 30 mg: 40/1,555 (2.6%) RR: 1.31 (0.87, 1.90)</td>
<td>Aspirin 283 mg: 1,576 (15.2%); Aspirin 30 mg: 1,555 (14.7%) RR: 1.04 (0.88, 1.23)</td>
<td>Aspirin 283 mg: 240/1,576 (15.2%); Aspirin 30 mg: 228/1,555 (14.7%) RR: 1.04 (0.88, 1.23)</td>
<td></td>
</tr>
<tr>
<td>Bousser et al</td>
<td>Aspirin 225 mg/d</td>
<td>D-A: 202/202; Aspirin: 198/198</td>
<td>3 yr</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>17 patients had stroke but the article does not classify to which group they belong</td>
</tr>
</tbody>
</table>

**Table 3—Randomized trials of Antiplatelet Agents for the Secondary Prevention of Noncardioembolic Stroke: Clinical Description and Results (Section 4.0)**

**Notes:**
- Composite Primary Outcome: Nonfatal episodes of bleeding were considered major if a hospital visit and treatment were necessary.
- Aspirin 283 mg: 240/1,576 (15.2%); Aspirin 30 mg: 228/1,555 (14.7%) RR: 1.04 (0.88, 1.23).
<table>
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<tr>
<th>Author/yr</th>
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<th>Composite Primary Outcome, No./Total (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diener et al125/1996</td>
<td>D-A: Dipyridamole 400 mg/d + Aspirin 50 mg/d; D-A: Dipyridamole 400 mg/d + Aspirin 50 mg/d; D-A: 1,650/1,650; Aspirin 1,649/1,649</td>
<td>2 yr</td>
<td>Severe or fatal</td>
<td>D-A: 18/1650 (1.1%); Aspirin: 182/1,649 (11.0%)</td>
<td>D-A: 102 (0.64, 1.23)</td>
<td>D-A: 185/1650 (1.2%); Aspirin: 20/1,649 (1.2%)</td>
<td>Major bleeding: all intracranial bleeding, any fatal bleeding, or any bleeding requiring hospital admission</td>
</tr>
<tr>
<td>ESPRIT Study Group120/2006</td>
<td>D-A: Dipyridamole 400 mg/d + Aspirin 30 – 325 mg/d; D-A: 1,363/1,363; Aspirin: 1,376/1,376</td>
<td>5 yr</td>
<td>RR: 0.67 (0.44, 1.01)</td>
<td>D-A: 93/1,363 (6.8%); Aspirin: 107/1,376 (7.8%)</td>
<td>D-A: 98 (0.67, 1.15)</td>
<td>D-A: 149/1,363 (10.9%); Aspirin: 192/1,376 (13.9%)</td>
<td></td>
</tr>
<tr>
<td>Hass et al144/1989</td>
<td>Ticlopidine 500 mg/d; Ticlopidine: 1,529/1,529; Aspirin: 1,540/1,540</td>
<td>6 yr</td>
<td>Ticlopidine: 0/1,529 (0%); Aspirin: 0/1,540 (0%)</td>
<td>D-A: 175/1,529 (11.4%); Aspirin: 196/1,540 (12.7%)</td>
<td>D-A: 90 (0.74, 1.09)</td>
<td>D-A: 349/1,540 (22.7%)</td>
<td></td>
</tr>
<tr>
<td>Gorelick et al147/2003</td>
<td>Ticlopidine 500 mg/d; Ticlopidine 902/902; Aspirin 907/907</td>
<td>2 yr</td>
<td>Ticlopidine: 10/902 (1.1%); Aspirin: 0.5 (0.25, 1.13)</td>
<td>D-A: 40/907 (4.4%); Aspirin: 1.13 (0.75, 1.71)</td>
<td>D-A: 90 (0.77, 1.01)</td>
<td>D-A: 133/902 (14.7%)</td>
<td></td>
</tr>
<tr>
<td>Gent et al145/1989</td>
<td>Ticlopidine 500 mg/d; Placebo: 528/528</td>
<td>3 yr</td>
<td>Ticlopidine: 2/525 (0.4%); Placebo: 1.2 (0.25, 1.13)</td>
<td>D-A: 64/525 (12.2%); Placebo: 64/528 (12.1%)</td>
<td>D-A: 2.01 (0.18, 22.12)</td>
<td>D-A: 106/525 (20.2%); Placebo: 134/528 (25.4%)</td>
<td></td>
</tr>
<tr>
<td>Matias-Guán et al147/2003</td>
<td>Aspirin 325 mg/d; Triflusal 600 mg/d</td>
<td>3 yr</td>
<td>Triflusal: 13/1,055 (1.2%); Aspirin: 1.052/1,052 (1.2%)</td>
<td>D-A: 68/1,055 (6.4%); Aspirin: 57/1,052 (5.4%)</td>
<td>D-A: 0.42 (0.22, 0.79)</td>
<td>D-A: 106/1,052 (12.4%)</td>
<td>Major systemic hemorrhage: bleeding episode requiring hospital admission and/or blood transfusion</td>
</tr>
</tbody>
</table>

*Table does not include trials of only aspirin vs placebo or the CAPRIE trial. The results of CAPRIE are presented in section 4.1. C-A = clopidogrel plus aspirin; D-A = dipyridamole plus aspirin; major bleeding = requiring transfusion or hospitalization or resulting in death; Composite primary outcome = death from all vascular causes, nonfatal stroke, nonfatal myocardial infarction.
of suffering a minor stroke or TIA. Half were treated with 650 mg of aspirin twice daily and half with 250 mg of ticlopidine twice daily. The ticlopidine group had a 21% RRR for stroke compared with aspirin, and a 9% reduction in the end point cluster of stroke, myocardial infarction, or vascular death at 3 years.146

Serious GI adverse effects (eg, ulcers and bleeding) were 2.5 times more common in the aspirin group even though patients who had any history of GI hemorrhage or dyspeptic symptoms were excluded from the trial. Two percent of the patients taking ticlopidine were unable to tolerate the medication because of diarrhea and another 2% because of skin rash. Severe neutropenia occurred in 0.9% of patients in the ticlopidine-treated group. Neutropenia reversed with cessation of treatment and almost always occurred within 2 to 3 months after treatment began. Because of the high incidence of neutropenia, however, blood counts are required at 2-week intervals for the first 3 months of ticlopidine therapy.

The Canadian American Ticlopidine Study (CATS) involved 1,072 patients who were enrolled after the occurrence of a major ischemic stroke.145 The patients were randomly allocated to 250 mg of ticlopidine twice daily or matching placebo. Patients in this study who received placebo had an event rate for stroke, myocardial infarction, or vascular death of 15.3%/yr, demonstrating the seriousness of stroke as a predictor of subsequent vascular events. Ticlopidine reduced the RR of stroke, myocardial infarction, or vascular death by 23% (p = 0.020) in the ticlopidine group. Adverse effects were similar to those noted in TASS. In the African American Antiplatelet Stroke Prevention Study, ticlopidine was compared with aspirin for secondary stroke prevention in 1,800 African American stroke/TIA patients.147 This study did not demonstrate a benefit of ticlopidine over aspirin.

Taken together, these trials show that ticlopidine reduces the risk of stroke and other vascular outcomes in patients with cerebrovascular disease. Ticlopidine is associated with an approximately 1% incidence of severe neutropenia and > 60 cases of ticlopidine-associated thrombotic thrombocytopenia purpura have been reported.148,149

Clopidogrel: Clopidogrel also is a thienopyridine that blocks the P2Y12 ADP receptor. Its anti-thrombotic effects were evaluated in the CAPRIE Study.150 CAPRIE was a randomized, blinded, multicenter trial designed to assess the relative efficacy of clopidogrel (75 mg/d) and aspirin (325 mg/d) in reducing the risk of the composite outcome of ischemic stroke, myocardial infarction, or vascular death, and to determine their relative safety. Three groups of patients were studied; those with recent ischemic stroke, recent myocardial infarction, and symptomatic peripheral arterial disease.

In 19,185 patients (> 6,000 in each of the three groups), the intention-to-treat analysis showed that patients treated with clopidogrel experienced a 5.32% annual risk of ischemic stroke, myocardial infarction, or vascular death, vs 5.83% with aspirin, for a RRR of 8.7% in favor of clopidogrel (95% CI, 0.3–16.5; p = 0.043), and an absolute risk reduction of 0.5%/yr. When serious hemorrhages were considered along with the primary outcome cluster in an intent-to-treat analysis, the RRR with clopidogrel was 9.5% (95% CI, 1.2–18.5). Finally, when the results in CAPRIE are analyzed using the Anti-thrombotic Trialists' technique (ie, intent-to-treat; all stroke, myocardial infarction, or vascular death, including hemorrhagic) and by relative odds reduction, there is a reduction of 10% favoring clopidogrel. For the 6,431 patients entered into CAPRIE with a stroke as the qualifying condition, the RRR for ischemic stroke, myocardial infarction, or vascular death was 7.3% (95% CI, −5.7 to 18.7; p = 0.26), and the RRR for the end point of stroke was 8% (95% CI, −7 to 21; p = 0.28).

Although there were no major differences between aspirin and clopidogrel in terms of safety, and adverse experiences were minimal, serious hemorrhages occurred at a slightly higher rate among patients taking aspirin (1.55% vs 1.38%). The overall safety profile of clopidogrel is similar to that of 325 mg/d of aspirin.

A key issue in interpreting CAPRIE is whether one can apply the point estimate and CI derived from the entire population (RRR 8.7% in favor of clopidogrel, 95% CI, 0.3–16.5; p = 0.043) to each of the three individual subpopulations (stroke, myocardial infarction, and peripheral arterial disease) included in the study. Although the primary outcome of CAPRIE was the cluster of ischemic stroke, myocardial infarction, and vascular death in all patients entered, the RRRs in the three subpopulations (approximately 3% in coronary, 22% in peripheral, and 8% in cerebrovascular patients) are different. On this basis, we choose to make inferences about the relative efficacy of clopidogrel vs aspirin largely on the basis of the results of the patients enrolled because of a recent stroke (n = 6,431).

The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study investigated the safety and efficacy of clopidogrel plus aspirin in patients with acute coronary syndromes.151 This study of 12,562 randomized patients found that the clopidogrel plus aspirin group showed a 20% RRR in the primary outcome of nonfatal myocardial infarction, stroke, or vascular death when compared with aspirin plus placebo. There was a relative reduction
in stroke of 14% in favor of the combination therapy, however, there were only a total of 162 strokes in the study and benefit was not statistically significant. Bleeding complications in this study were increased on combination therapy, but it is not known how much bleeding will occur in cerebrovascular patients.

The MATCH trial was a randomized, blinded, placebo-controlled trial to compare aspirin (75 mg/d) with placebo in 7,599 high-risk patients with recent ischemic stroke or TIA and at least one additional vascular risk factor who were already receiving clopidogrel 75 mg/d. The duration of treatment and follow-up was 18 months. The primary endpoint was a composite of ischemic stroke, myocardial infarction, vascular death, or rehospitalization for acute ischemia (including rehospitalization for TIA, angina pectoris, or worsening of peripheral arterial disease). Analysis was by intention to treat; 596 patients (15.7%) reached the primary endpoint in the group receiving aspirin and clopidogrel compared with 636 (16.7%) in the clopidogrel alone group (RRR 6.4%, [95% CI, 4.6–16.3]; absolute risk reduction 1% [-0.6 to 2.7]). Life-threatening bleeds were higher in the group receiving aspirin and clopidogrel vs clopidogrel alone (96% [2.6%] vs 49% [1.3%]; absolute risk increase 1.3% [95% CI, 0.6–1.9] over 18 months). Major bleeds were also increased in the group receiving aspirin and clopidogrel, but there was no difference in mortality. MATCH showed that adding aspirin to clopidogrel in high-risk patients with recent ischemic stroke or TIA is associated with a nonsignificant difference in reducing major vascular events. The risk of life-threatening or major bleeding is increased by the addition of aspirin.

The CHARISMA trial assigned 15,603 patients with either clinically evident cardiovascular disease or multiple risk factors to receive clopidogrel (75 mg/d) plus low-dose aspirin (75 to 162 mg/d) or placebo plus low-dose aspirin and followed them for a median of 28 months. The primary efficacy endpoint was a composite of myocardial infarction, stroke, or death from cardiovascular causes.

The rate of the primary efficacy endpoint was 6.8% with clopidogrel plus aspirin vs 7.3% with placebo plus aspirin (RR, 0.93; 95% CI, 0.83–1.05; p = 0.22). The respective rates of the principal secondary efficacy endpoint, which included hospitalizations for ischemic events, was 16.7% and 17.9% (RR, 0.92; 95% CI, 0.86–0.995; p = 0.04), and the rates of severe bleeding were 1.7% and 1.3% (RR, 1.25; 95% CI, 0.97–1.61; p = 0.09). The rate of the primary endpoint in the subgroup of 3,284 patients with multiple risk factors was 6.6% with clopidogrel and 5.5% with placebo (RR, 1.2; 95% CI, 0.91–1.59; p = 0.20), and the rate of death from cardiovascular causes also was higher with clopidogrel (3.9% vs 2.2%, p = 0.01). In the large subgroup of 12,153 patients with clinically evident atherothrombosis, the rate was 6.9% with clopidogrel and 7.9% with placebo (RR, 0.85; 95% CI, 0.77–0.998; p = 0.046). In CHARISMA, the 5,835 patients who entered with documented cerebrovascular disease experienced a 13.9% RRR in the rate of myocardial infarction, stroke, or death from cardiovascular causes favoring dual antiplatelet therapy. This benefit was not statistically significant (p = 0.13).

Dipyridamole: The Antithrombotic Trialists analyzed all trials involving dipyridamole alone vs placebo and dipyridamole combined with aspirin vs placebo, including ESPS-2 that used an extended-release formulation of dipyridamole. Fifteen trials compared dipyridamole alone vs placebo and showed a 16% odds reduction for stroke, myocardial infarction, or vascular death favoring dipyridamole. Forty-six trials compared dipyridamole combined with aspirin vs placebo and showed a 30% odds reduction in stroke, myocardial infarction, or vascular death favoring the combination.

In the second European Stroke Prevention Study (ESPS-2) patients who had experienced either an ischemic stroke or TIA were enrolled in a multicenter, randomized, blinded, factorial, placebo-controlled trial with four treatment groups and a 2-year follow-up for all patients. The four twice-daily treatments were 25 mg aspirin; 200 mg extended-release dipyridamole; 25 mg aspirin plus 200-mg extended-release dipyridamole; and placebo. A total of 6,602 patients were included in the analysis, and the outcome event clusters were fatal or nonfatal stroke, stroke or death from any cause, and all-cause mortality. The study showed that both extended-release dipyridamole (200 mg bid) and aspirin (25 mg bid) had an independent and statistically significant effect in reducing the risk of stroke recurrence (16% and 18%, respectively, when compared with placebo). The study also showed that the combination of extended-release dipyridamole plus aspirin compared to aspirin alone reduced the RR of stroke (nonfatal and fatal) by 23%. The absolute risk reduction was 3% at 2 years, or about 1.5% annually.

The ESPRIT study was a randomized trial in which patients were assigned to aspirin (30–325 mg/d) with (n = 1,363) or without (n = 1,376) dipyridamole (200 mg bid) within 6 months of a TIA or minor stroke of presumed arterial origin. The primary outcome event was the composite of death from all vascular causes, nonfatal stroke, nonfatal myocardial infarction, or major bleeding complication, whichever happened first. Treatment was not blinded, but adjudicating of outcome events was blinded. Primary analysis was by intention to treat.
Mean follow-up was 3.5 years. Median aspirin dose was 75 mg in both treatment groups (range, 30–325 mg); extended-release dipyridamole was used by 83% (n = 1,131) of patients on the combination regimen. Primary outcome events arose in 173 patients (13%) receiving aspirin and dipyridamole and in 216 patients (16%) receiving aspirin alone (hazard ratio, 0.80; 95% CI, 0.66–0.98; absolute risk reduction, 1.0%/yr; 95% CI, 0.1–1.8). Addition of the ESPRIT data to the metaanalysis of previous trials resulted in an overall risk ratio for the composite of vascular death, stroke, or myocardial infarction of 0.82 (95% CI, 0.74–0.91). Patients receiving aspirin and dipyridamole discontinued trial medication more often than those receiving aspirin alone (470 vs 184), mainly because of headache. ESPRIT limitations include that it was open-label, used 30 mg of aspirin in nearly half the patients, and many patients discontinued treatment because of headaches. The Appendix summarizes the evidence from randomized trials of dipyridamole plus aspirin vs aspirin for secondary stroke prevention.

Other Agents: Other antiplatelet agents, including trifusul and cilostazol, have been tested in the setting of secondary stroke prevention (Table 3). Sufficient data are not currently available to make recommendations regarding the use of these agents for stroke prevention.

In summary, aspirin reduces the odds of the composite outcome of stroke, myocardial infarction, or vascular death in all high-risk patients with symptomatic atherosclerosis by about 23%. It reduces the odds of stroke alone by about 25%. In trials limited to stroke/TIA patients, aspirin reduced the odds of this composite outcome by only 16%. In stroke/TIA patients, ticlopidine is more effective than placebo. It reduces the RR of stroke, myocardial infarction, or vascular death by about 23%. Ticlopidine has at least a 5% incidence of bothersome adverse effects, a 0.9% incidence of severe neutropenia, and a small risk of ticlopidine-associated thrombotic thrombocytopenia purpura. The serious side effects of ticlopidine have led most experts to abandon its use. In stroke patients, clopidogrel appears to be more effective than aspirin for prevention of stroke or the outcome cluster of stroke, myocardial infarction, or vascular death. The safety profile of clopidogrel is comparable to aspirin and safer than ticlopidine. The combination of clopidogrel plus aspirin is not generally recommended for stroke/TIA patients because of the high bleeding risk over the long-term. Compared with aspirin, the combination of dipyridamole plus aspirin in stroke/TIA patients produces about an 18% reduction in stroke, myocardial infarction, and vascular death without a significant increase in bleeding. The recommendation below, to use the combination of aspirin and extended-release dipyridamole (25/200 mg bid) over aspirin should not be construed to imply a new standard for control groups in future stroke prevention trials, nor a “standard of care” for clinical practice.

The PROFESS (Prevention Regimen for Effectively Avoiding Second Strokes) trial directly compared the combination of extended-release dipyridamole plus aspirin vs clopidogrel.156

The results of this large study that included 20,332 stroke patients were presented in May 2008, just prior to publication of the ACCP guidelines. The risk of recurrent stroke was similar in the two treatment groups, and the risk of the composite outcome of stroke, myocardial infarction, and vascular death was identical. Major hemorrhagic events, including intracranial bleeds, were more common in the extended-release dipyridamole-plus-aspirin group. Any impact of these results on the recommendations will be addressed in the next update to the ACCP guidelines.

To our knowledge, no clinical trials have directly addressed the issue of subsequent therapy for patients who experience recurrent episodes of brain ischemia while taking an antiplatelet drug. Many experts select an alternative antiplatelet drug.

Cost-effectiveness: Since aspirin is inexpensive and alternative antiplatelet agents are relatively expensive, a key resource question is whether the more expensive agents are worth the cost. Since the lifetime cost of stroke is high (and thus the potential cost savings of stroke prevented is high), even a modestly effective drug that is not inordinately more expensive is not only a good tradeoff of cost for health benefits, it may even be cost saving.157,158

This tradeoff can be demonstrated roughly by considering per patient cost of 1 year of treatment vs per patient costs avoided (costs of stroke that would not occur in the year of treatment, because of treatment). The former costs are based on the market prices for pharmaceuticals. The latter costs can be estimated by the lifetime cost of stroke divided by the Numbers Needed to Treat (NNT = 1/absolute risk reduction) obtained from clinical trials. For example, if the lifetime cost of stroke is $100,000159,160 and the absolute risk reduction attributable to a particular drug vs its next less expensive comparator is 0.5% (ie, NNT is 200), then per patient avoided stroke costs are $100,000/200 = $500. This suggests that if the additional cost of a drug under consideration is less than $500 then the treatment would be cost saving. If the absolute risk reduction were better, say 1% (NNT100), a treatment with an extra cost below $1,000 would lead to a net cost saving. If the lifetime cost of stroke is actually less, say $50,000, then below a threshold
value of $250 extra cost, the more expensive treatment would be cost saving.

There are two practical problems with this formulation. First, it is based on a societal perspective in which all costs are equally relevant. The value may be quite different from a local perspective where pharmacy costs are salient, but long-term care costs are not. Second, in an environment in which other stroke prevention treatments are being used at less than optimal levels, the relevant alternative to aspirin may not be a relatively expensive antiplatelet agent, but rather other drugs such as antihypertensive or lipid lowering agents. While they all may be cost effective (or even cost saving) from a societal perspective, a relatively expensive antiplatelet agent may not be the most crucial unmet need.

Recommendations

4.1.1. In patients who have experienced a noncardioembolic stroke or TIA (ie, atherothrombotic, lacunar or cryptogenic), we recommend treatment with an antiplatelet drug (Grade 1A). Aspirin, the combination of aspirin, 25 mg and extended-release dipyridamole, 200 mg bid, and clopidogrel (75 qd) are all acceptable options for initial therapy. We recommend an aspirin dose of 50 to 100 mg/d over higher aspirin doses (Grade 1B).

4.1.2. In patients who have experienced a noncardioembolic stroke or TIA, we recommend using the combination of aspirin and extended-release dipyridamole (25/200 mg bid) over aspirin (Grade 1A) and suggest clopidogrel over aspirin (Grade 2B).

Underlying values and preferences: The implementation of the recommendation to use the combination of aspirin and extended-release dipyridamole over aspirin may vary based on cost, tolerability, availability, ease of use, and absolute risk.

4.1.3. In most patients with a noncardioembolic stroke or TIA, we recommend avoiding long-term use of the combination of aspirin and clopidogrel (Grade 1B). In those with a recent acute myocardial infarction, other acute coronary syndrome, or a recently placed coronary stent, we recommend clopidogrel plus aspirin (75 to 100 mg) [Grade 1A]. The optimal duration of dual antiplatelet therapy depends on the specific cardiac indications (see other articles in the supplement).

4.1.4. For patients who are allergic to aspirin, we recommend clopidogrel (Grade 1A).

4.2 Prevention of Noncardioembolic Cerebral Ischemic Events: Oral Anticoagulants

Several large, well-designed, randomized trials have assessed the efficacy of oral anticoagulants for secondary prevention of noncardioembolic stroke (including strokes of large artery, small penetrating artery, and unknown cause). One large, randomized trial compared high-intensity oral anticoagulation (INR, 3.0 to 4.5) with aspirin (30 mg/d) in 1,316 patients. This study was stopped prematurely because of a significant excess in the rate of major bleeding complications (including 27 intracranial hemorrhages) in the anticoagulation group. Because of early termination, the comparative efficacy of anticoagulation vs aspirin for prevention of cerebral ischemic events could not be determined. The incidence of major bleeding complications in this study increased sharply with increasing intensities of anticoagulation (for each 0.5 INR unit, the incidence of major bleeding increased by a factor of 1.4). Clearly, an INR range of 3.0 to 4.5 is not safe for secondary prevention of noncardioembolic stroke.

The Warfarin Aspirin Recurrent Stroke Study (WARSS) investigated whether warfarin would prove superior in the prevention of recurrent ischemic stroke in patients with a prior noncardioembolic ischemic stroke. WARSS was a randomized trial that compared the effect of warfarin (at a dose adjusted to produce an INR of 1.4 to 2.8) to that of aspirin (325 mg/d) on recurrence of ischemic stroke or death from any cause within 2 years. No significant differences were found between the treatments in any of the outcomes measured. Also, there were no significant treatment-related differences in the frequency of or time to the primary end point or major hemorrhage according to the cause of the initial stroke. Subgroup analyses of this study failed to find a benefit of warfarin over aspirin for patients with PFO, antiphospholipid antibodies, or posterior circulation strokes. In addition, patients who were taking aspirin at the time of their initial stroke did not benefit from warfarin over aspirin.

The Warfarin vs Aspirin for Symptomatic Intracranial Disease (WASID) was a randomized blinded study that compared warfarin (target INR, 2–3) with aspirin (1,300 mg/d) for preventing stroke (ischemic and hemorrhagic) and vascular death in patients with symptomatic stenosis of a major intracranial artery. This study was stopped prematurely by the safety monitoring committee after 569 patients were enrolled because warfarin was associated with significantly higher rates of adverse events and provided no benefit over aspirin.

More recently, the European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT)
compared oral anticoagulation (target INR, 2–3; n = 536) with aspirin (30–325 mg/d; n = 532) in patients with TIA or minor stroke of presumed arterial origin. The primary outcome was death from all vascular causes, nonfatal stroke, nonfatal myocardial infarction, or major bleeding complication. A primary outcome event occurred in 19% of the patients on anticoagulants and in 18% of the patients on aspirin. These results provided further confirmation that warfarin is no more effective than aspirin for patients with noncardioembolic stroke.

Carotid and Vertebral Artery Dissections: Dissections of the carotid or vertebral cervical arteries may occur spontaneously or as a result of trauma, ranging from trivial to severe in nature. Stroke mechanisms associated with dissections include intraluminal thrombus formation with distal embolization, clot propagation, or hemodynamic infarction due to critical arterial stenosis or occlusion. Intracranial dissections are much less common than cervical artery dissections and may cause either ischemic or hemorrhagic stroke, including subarachnoid hemorrhage.

Antithrombotic stroke prevention strategies in patients with cervical artery dissections include anticoagulation often initially with IV heparin followed by warfarin oral anticoagulation, or antiplatelet therapy. To our knowledge, no randomized controlled trials have been conducted comparing anticoagulation with antiplatelet therapy. The necessity for, and duration of, antithrombotic therapy following a dissection has not been established although the majority of ischemic strokes occur within the first days or weeks of the dissection. A Cochrane systematic review of case series and clinical studies did not establish any significant difference between anticoagulation and antiplatelet therapy.

Recommendation

4.2.1. For patients with noncardioembolic stroke or TIA, we recommend antiplatelet agents over oral anticoagulation (Grade 1A).

Remark: Some experts recommend oral anticoagulants for specific patient populations with noncardioembolic stroke, including patients with cervical artery dissection (see above), severe carotid stenosis prior to endarterectomy, antiphospholipid antibody syndrome, symptomatic intracranial large-artery stenosis, and coagulation factor deficiencies. Whether anticoagulants are superior to antiplatelet agents for these indications is unknown.

4.3 Prevention of Cerebral Ischemic Events in Patients Undergoing Carotid Endarterectomy: Antiplatelet Agents

One randomized trial—the ASA and Carotid Endarterectomy (ACE) trial—has addressed this issue. See Section 4.1 for the evidence summary.

Recommendation

4.3. In patients undergoing carotid endarterectomy, we recommend aspirin (50–100 mg/d) prior to and following the procedure (Grade 1A).

4.4 Prevention of Cardioembolic Cerebral Ischemic Events

Atrial fibrillation is the most common cause of cardiac embolism and is responsible for about 50% of all cardioembolic emboli. In addition, several other cardiac lesions can cause cardioembolic stroke. Other high-risk sources of cardioembolic embolism include mitral stenosis, mechanical prosthetic valves, recent myocardial infarction, left ventricular mural thrombus, atrial myxoma, dilated cardiomyopathies, infective endocarditis, and marantic endocarditis.

The cause of 30 to 40% of all ischemic strokes remains undetermined, and cardiac mechanisms are suspected to account for a substantial percentage of these cryptogenic strokes. Advances in cardiac imaging now permit the frequent detection of additional potential cardiac sources of emboli, such as PFO, atrial septal aneurysm, aortic arch atheroma, and mitral valvular stenosis.

The diagnosis of cardioembolic stroke has been traditionally based on the detection of a potential cardiac source in a patient with an abrupt-onset nonlacunar stroke syndrome without a coexisting significant vascular mechanism. However, clinical features such as the mode of onset (sudden or progressive) or the vascular territory involved are not sufficiently specific or sensitive indicators to establish the stroke mechanism. Rapid recovery from major hemispheric deficits or presentation with depressed level of consciousness is suggestive of cardioembolic stroke. The occurrence of multiple infarctions in different vascular territories or the history of systemic emboli increases the likelihood of a cardiac mechanism. Many patients with a potential cardiac source may also have concomitant vascular disease. Early angiographic demonstration of an embolic occlusion may be helpful to support the diagnosis and to exclude atherosclerotic disease and other arterial causes. Transesophageal echocardiography is more sensitive for detecting cardioembolic sources than transthoracic studies, particularly when searching for left atrial sources, atrial septal
defects, and aortic atheroma. Because the risks of stroke and recurrent embolic events vary with different cardiac disorders, it is clinically useful to divide potential cardiac sources into high- and low-risk categories (Table 4).

### 4.4.1 Patients With Stroke and Underlying Atrial Fibrillation: Anticoagulation

Oral anticoagulant therapy is highly effective for both primary and secondary prevention of stroke in patients with atrial fibrillation (see article on “Antithrombotic Therapy in Atrial Fibrillation”). Patients who have already suffered a stroke are at high risk of subsequent cardioembolic emboli. Adequate data are not available to address the issue of when to begin oral anticoagulation following a cardioembolic stroke. In the European Atrial Fibrillation Trial, patients with recent stroke or TIA and atrial fibrillation were treated with oral anticoagulation. In about half of the patients, anticoagulation was initiated within 2 weeks after symptom onset. No increase in brain hemorrhage was apparent in patients treated early vs later. In general, we recommend initiation of oral anticoagulation therapy within 2 weeks of a cardioembolic stroke; however, for patients with large infarcts or other risk factors for hemorrhage, additional delays may be appropriate.

**Recommendation**

4.4.1. In patients with atrial fibrillation who have suffered a recent stroke or TIA, we recommend long-term oral anticoagulation (target INR, 2.5; range, 2.0 to 3.0) [Grade 1A].

### 4.4.2 Patients With Stroke With Underlying Atrial Fibrillation: Antiplatelet Agents

In general, studies of antiplatelet agents for stroke prevention have focused on patients with TIAs or strokes of atherothrombotic (noncardioembolic origin). Many of these studies specifically excluded patients with high-risk sources of cardiac embolism, such as atrial fibrillation. To our knowledge, only two large randomized studies have specifically evaluated the efficacy of antiplatelet agents for secondary prevention of cardiac embolism. The European Atrial Fibrillation Trial (EAFIT) compared the efficacy of aspirin (300 mg/d) to placebo in patients with atrial fibrillation who had suffered a stroke or TIA within the last 3 months. In this trial, aspirin was associated with a 16% reduction in the RR of stroke; however, this difference was not statistically significant. The Studio Italiano Fibrillazione Atrial (SIFA) study compared the efficacy of indobufen (a reversible inhibitor of cyclooxygenase) with warfarin (INR, 2.0 to 3.5) among 916 atrial fibrillation patients who had experienced a nondisabling stroke or TIA within the last 15 days. No significant difference in the incidence of stroke, myocardial infarction, PE, or vascular death was noted between the two groups; however, the power of the study was not large enough to exclude a substantial difference between the efficacies of the two agents. Therefore, at present, only very limited data are available directly addressing the efficacy of antiplatelet agents for secondary prevention of cardioembolism. Randomized trials of aspirin in patients with atrial fibrillation who have not yet had a stroke suggest a RRR of approximately 25% and provide further indirect evidence in support of antiplatelet agents in patients with cardioembolic stroke.

The combination of aspirin and clopidogrel was compared to warfarin in the ACTIVE trial. Atrial fibrillation patients with at least one risk factor for stroke were randomized to receive oral anticoagulation therapy (target INR, 2.0–3.0; n = 3,371) or clopidogrel (75 mg/d) plus aspirin (75–100 mg/d; n = 3,335). The study was stopped early because of clear evidence of superiority of oral anticoagulation (RR, 1.44 [1.18–1.76]; p = 0.0003).

**Recommendation**

4.4.2. For patients with cardioembolic stroke who have contraindications to anticoagulant therapy, we recommend aspirin at a dose of 75 to 325 mg/d (Grade 1B).

Remark: See atrial fibrillation article for discussion and recommendations regarding the dose of aspirin for patients with atrial fibrillation.

### 4.4.3 Patients With Aortic Atheromata

Mounting evidence implicates complex atherosclerotic aortic plaques as a significant independent risk factor for embolic stroke. Trans-
esophageal echocardiography is able to visualize atherosclerotic disease of the thoracic aorta. Plaques of $>4$ to $5$ mm in thickness, ulcerated plaques, and those with mobile components are more likely to be associated with stroke. In one study, the annual risk of stroke was $33\%$ in patients with protruding plaques of $\geq 5$ mm in the thoracic aorta, compared with $7\%$ in matched controls. Another study followed 331 consecutive stroke patients prospectively for a mean of 2.4 years. The annual stroke rate was $11.9\%$ in the 45 patients with plaques $\geq 4$ mm thick, compared with $3.5\%$ in 143 patients with lesser degrees of plaque thickness and $2.8\%$ in the 143 patients with no significant aortic plaque ($p < 0.001$). This high risk of neurologic and vascular events in stroke patients with significant aortic atherosclerosis has been confirmed by two recent prospective studies and a metaanalysis.

To our knowledge, no randomized trials have evaluated the role of any antithrombotic therapies in patients with aortic atheroma. Two studies showed a benefit of an oral anticoagulant over aspirin in patients with mobile thrombi in the aortic arch, but the studies were retrospective and nonrandomized. Furthermore, hemorrhagic complications possibly outweighed the benefits of the anticoagulants. One other retrospective study of 519 patients with aortic plaques $>4$ mm found that statins ($0.39$ [$0.24–0.62$, $p = 0.0001$]), but not oral anticoagulation ($1.18$ [$0.91–1.54$, $p = 0.21$]) or antiplatelet therapy ($0.77$ [$0.51–1.15$, $p = 0.20$]) had a significant protective effect against recurrent embolism. Concerns also exist regarding the possibility of anticoagulation increasing the risk of cholesterol embolism in these patients. One randomized study is in progress comparing oral anticoagulant to antiplatelet therapy in patients with plaques $>4$ mm in the thoracic aorta.

Recommendation

4.4.3. In patients with stroke associated with aortic atherosclerotic lesions, we recommend antiplatelet therapy over no therapy (Grade 1A).

For patients with cryptogenic stroke associated with mobile aortic arch thrombi, we suggest either oral anticoagulation or antiplatelet agents (Grade 2C).

4.4.4 Patients With PFO

A PFO is detected by contrast echocardiography in about 20% of normal individuals. In young stroke patients, PFOs are detected in about 40%, and in young patients with otherwise cryptogenic stroke, the rate of PFO detection may be 50% or more. In a case-control study, 100 consecutive stroke patients $<55$ years old were compared with 55 control subjects. PFO was significantly associated with stroke, occurring in 43% of stroke patients, 56% of the patients with cryptogenic stroke, and only 18% of controls (OR, 3.9; 95% CI, 1.5–10). A PFO provides a conduit permitting a thrombus arising from the venous circulation to pass from right to left through the heart, resulting in a stroke. In the absence of a venous source of thromboembolism or a coexisting pulmonary embolus, the diagnosis remains presumptive and rests on the detection of a PFO with significant capability for right-to-left shunt in a patient with no other identified stroke mechanisms. Other mechanisms of thromboembolism may also be involved if the PFO is associated with an atrial septal aneurysm or atrial fibrillation or flutter. Among stroke patients with PFOs, the risk of stroke recurrence is estimated to be only $1$ to $2\%/yr$. Patients with complex PFOs (eg, the combination of a large PFO and atrial septal aneurysm) may be at substantially higher risk for recurrent events. One follow-up study on patients $<55$ years old with cryptogenic stroke who all hadTEE evaluation of septal abnormality showed that the risk of recurrent stroke was 0% in patients with atrial septal aneurysm, $0.6%/yr$ in patients with PFO, $1%/yr$ in patients with no septal abnormalities, and $4.0%/yr$ in patients with both PFO and atrial septal aneurysm while on aspirin 300 mg/d. In the PICSS trial, stroke patients with PFO did not have a significantly increased 2-year risk of recurrent stroke or death compared to those without a PFO, and there was no significant difference in the 2-year event rates among those treated with warfarin vs aspirin. Cryptogenic stroke patients with or without a PFO had slightly lower risk of recurrent stroke and death from all causes while on warfarin compared to patients on aspirin, but this result was not significant.

PFO closure is an alternative to antithrombotic therapy for the long-term prevention of recurrent PFO-related stroke. PFO closure may be achieved by surgery or with a percutaneous catheter-delivered closure device. Surgical closure is effective for eliminating the shunt but involves an open-heart operation with the inherent costs and the potential for surgical complications. The rate of recurrent stroke after surgical closure varies from $0–4%/yr$. Percutaneous closure is technically feasible and has the potential to avoid major surgical morbidity. Stroke recurrence rates in published reports are $<4%/yr$. A number of devices are presently in clinical use, although to date none has been granted Food and Drug Administration approval. Clinical trials are in progress to evaluate the safety and
efficacy of percutaneous closure. For patients with an ischemic stroke and a PFO in combination with other risk factors (such as hypercoagulability, atrial septal aneurysm, previous cryptogenic brain infarcts, or TIAs), there are inadequate data available to make a recommendation regarding optimal medical therapy (anticoagulation or antiplatelet therapy) vs endovascular/surgical closure of the PFO.

Recommendation

4.4.4. In patients with cryptogenic ischemic stroke and a PFO, we recommend antiplatelet therapy over no therapy (Grade 1A) and suggest antiplatelet therapy over warfarin (Grade 2A). For patients with evidence of a DVT, we recommend anticoagulation (see “Antithrombotic Therapy for Venous Thromboembolic Disease” chapter).

4.4.5 Mitral Valve Strands and Prolapse

Mitral valve strands, also known as Lamb1 excrescences, are filamentous mobile processes attached to the mitral valve. These strands are also occasionally seen on the aortic valve on transesophageal echocardiography.201 Some studies have implicated these strands as a potential embolic source, but they do not seem to increase the risk of stroke recurrence and the therapeutic implications, if any, are unknown.202,203

Mitral valve prolapse was implicated as a potential source of embolic stroke in the 1970s.204 However, several case control studies in young stroke patients did not confirm this association using currently accepted echocardiographic criteria.185,205 Recent population-based prospective studies failed to find an increased risk of ischemic stroke associated with this common echocardiographic finding, and no randomized trial data are available.206,207

Recommendation

4.4.5. In patients with mitral valve strands or prolapse who have a history of TIA or stroke, we recommend antiplatelet therapy (Grade 1A).

4.4.6 Other Cardiac Sources

Anticoagulation is not indicated for patients with stroke caused by intracardiac tumors or septic emboli (other than those with mechanical heart valves; see article on “Antithrombotic Therapy in Mechanical and Biological Prosthetic Heart Valves”). Oral anticoagulation is also beneficial for prevention of recurrent stroke in patients with several other high-risk cardiac sources (see articles in this supplement on prosthetic heart valves, valvular heart disease, and coronary artery disease).

5.0 Cerebral Venous Sinus Thrombosis

Cerebral venous sinus thrombosis (CVST) has diverse clinical presentations, which may include headache, focal neurologic deficits, seizures, alterations of consciousness, and papilledema with a sudden or progressive onset.208 Diagnosis of the thrombosed sinus, although frequently suspected on CT scan, is based on increased signal on both T1- and T2-weighted MRI and MR angiography. Conventional angiography is rarely needed when MRI is available.209 Over 100 causes of CVST have been reported, and recent emphasis has been given to an increased risk in carriers of prothrombin and factor V gene mutations, which may be enhanced in women who are taking oral contraceptives.210 The prognosis of CVST is generally much better than previously thought, but remains largely unpredictable.

5.1 Anticoagulation for CVST

Two small, randomized trials have shown somewhat differing results.211,212 One randomized study compared dose-adjusted UFH (partial thromboplastin time at least 2 times control) to placebo in 20 patients, with both patients and observers blinded to the treatment, and was stopped early because of the efficacy of heparin. Among 10 patients receiving heparin, 8 patients recovered completely and two patients had slight residual neurologic deficits at 3 months, compared to one complete recovery, six neurologic deficits, and three deaths in the placebo group (p < 0.01).211 In the same publication, the authors reported an additional retrospective study of 43 CVST patients with intracranial bleeding, 27 of whom received dose-adjusted heparin. The mortality rate was 15% in the heparin group compared with 69% in the nonheparin group.211

The other randomized trial compared nadroparin (90 anti-Xa U/kg bid) to placebo for 3 weeks followed by an unblinded comparison between 3 months of oral anticoagulation for patients who received nadroparin and no antithrombotic therapy for the placebo group.210 Patients with intracranial bleeding caused by the CVST were also included. Overall, after 12 weeks, 13% (3 of 30 patients) in the anticoagulation group and 21% (6 of 29 patients) in the placebo group had a poor outcome, for an absolute benefit of 7% and a RRR of 38% in the nadroparin group, a difference which did not reach statistical significance. There were two fewer deaths in the nadroparin group (two vs four) and no new symptomatic cerebral hemorrhages. There were also twice as many patients with isolated intracranial hypertension in the placebo group (28% vs 13%) as in the nadroparin group, a subgroup of CVST patients who typically have a good outcome.

Based on the results of both randomized trials, a metaanalysis and the results from observational stud-
Both unfractionated and low-molecular-weight heparin are safe and probably effective in CVST. It is unlikely that a randomized trial with an adequate number of patients will be performed in the near future. We recommend heparin as first-line treatment, even in patients with hemorrhagic venous infarcts, followed by oral anticoagulation for a period of 3 to 6 months. Some experts do not recommend heparin for patients with large hemorrhagic venous infarcts with associated hematomas. In patients who demonstrate progressive neurologic deterioration despite adequate anticoagulation, other options such as local intrathrombus infusion of a thrombolytic agent together with IV heparin are under investigation.

**Recommendation**

5.1. In patients with venous sinus thrombosis, we recommend that clinicians use UFH (Grade 1B) or low-molecular-weight heparin (Grade 1B) over no anticoagulant therapy during the acute phase, even in the presence of hemorrhagic infarction. In these patients, we recommend continued use of vitamin K antagonist therapy for up to 12 months (target INR, 2.5; range, 2.0–3.0) [Grade 1B].

Remark: For patients with venous sinus thrombosis associated with heparin-induced thrombocytopenia, see article on heparin-induced thrombocytopenia for recommendations.
### Evidence Profile (Section 4.1)

#### Quality Assessment

<table>
<thead>
<tr>
<th>No. of Studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Consistency</th>
<th>Directness</th>
<th>Precision</th>
<th>Reporting Bias</th>
<th>Strength of Association</th>
<th>Dipyridamole Plus Aspirin</th>
<th>Aspirin</th>
<th>RR (95% CI)</th>
<th>Events Prevented per 1,000 Treated</th>
<th>Quality</th>
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<tr>
<td><strong>Recurrent stroke</strong></td>
<td>3*</td>
<td>Randomized controlled trial</td>
<td>No serious limitations</td>
<td>No important inconsistency</td>
<td>No problems</td>
<td>No imprecision</td>
<td>No reporting bias</td>
<td>No strong association</td>
<td>271/3,215 (8.4)</td>
<td>339/3,223 (10.5)</td>
<td>0.80 (0.69–0.93)</td>
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<td><strong>Major bleeding</strong></td>
<td>2†</td>
<td>Randomized controlled trial</td>
<td>No serious limitations</td>
<td>Some inconsistency</td>
<td>No problems</td>
<td>Some imprecision</td>
<td>No reporting bias</td>
<td>No strong association</td>
<td>62/3,013 (2.1)</td>
<td>73/3,025 (2.4)</td>
<td>0.92 (0.46–1.84)</td>
<td>Not significant</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>4¶</td>
<td>Randomized controlled trial</td>
<td>No serious limitations</td>
<td>No inconsistency</td>
<td>No problems</td>
<td>No imprecision</td>
<td>No reporting bias</td>
<td>No strong association</td>
<td>332/3,663 (9.1)</td>
<td>337/3,665 (9.2)</td>
<td>0.99 (0.85–1.14)</td>
<td>Not significant</td>
</tr>
<tr>
<td><strong>Composite primary outcome</strong></td>
<td>6††</td>
<td>Randomized controlled trial</td>
<td>No serious limitations</td>
<td>No inconsistency</td>
<td>No problems</td>
<td>No imprecision</td>
<td>No reporting bias</td>
<td>No strong association</td>
<td>522/3,888 (13.4)</td>
<td>636/3,907 (16.3)</td>
<td>0.82 (0.74–0.91)</td>
<td>29</td>
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</tbody>
</table>

¶One study favors dipyridamole plus aspirin; one favors aspirin.
§95% CI includes no effect.
‖95% CI includes no effect; events prevented per 1,000 treated not calculated.
§95% CI includes no effect, but not downgraded due to narrow CI.
**Includes death from all vascular causes; nonfatal stroke; nonfatal myocardial infarction; major bleeding.
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REFERENCES
1 Fieschi CAC, Lenzi GL. Clinical and instrumental evaluation of patients with ischemic stroke within the first six hours. J Neurol Sci 1989; 91:311–322
3 Fieschi C. Transient embolic occlusion of the middle cerebral and internal carotid arteries in cerebral apoplexy. J Neurol Neurosurg Psychiatry 1969; 32:236
15 Clark WM, Wissman S, Albers GW, et al. Recombinant tissue-type plasminogen activator (Alteplase) for ischemic stroke 3 to 5 hours after symptom onset: the ATLANTIS Study; a randomized controlled trial. Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke. JAMA 1999; 282:2019–2026
76 Sacco RL, Foulkes MA, Mohr JP, et al. Determinants of
79 Swanson RA. Intravenous heparin for acute stroke: what can we learn from the megatrials? Neurology 1999; 52:1746–1750
84 Fisher CM. Use of anticoagulants in cerebral thrombosis. Neurology 1958; 8:311–332
88 Haley EC Jr, Kassell NF, Torner JC. Failure of heparin to prevent progression in progressing ischemic infarction. Stroke 1988; 19:10–14
112 Cerebral Embolism Study Group. Immediate anticoagulation of embolic stroke: a randomized trial. Stroke 1983; 14:668–676
118 Adams HP Jr. Emergent use of anticoagulation for treat-


156 Diener HC, Sacco R, Yusuf S. Rationale, design and baseline data of a randomized, double-blind, controlled trial comparing two antithrombotic regimens (a fixed-dose combination of extended-release dipyridamole plus ASA with clopidogrel) and telmisartan versus placebo in patients with strokes: the Prevention Regimen for Effectively Avoiding Second Strokes Trial (PROFESS). Cerebrovasc Dis 2007; 23:368–380


163 Chimowitz MI. Warfarin vs Aspirin for Symptomatic Intracranial Disease (WASID). Stroke 2000; 31:562

164 Algra A. Medium intensity oral anticoagulants versus aspirin after cerebral ischemia of arterial origin (ESPRIT): a randomised controlled trial. Lancet Neurol 2007; 6:115–124


192 Cujec B, Mainra R, Johnson DH. Prevention of recurrent cerebral ischemic events in patients with patent foramen ovale and cryptogenic strokes or transient ischemic attacks. Antithrombotic and Thrombolytic Therapy 8th Ed: ACCP Guidelines


Ende DJ, Chopra PS, Rao PS. Transcatheter closure of atrial septal defect or patent foramen ovale with the buttoned device for prevention of recurrence of paradoxical embolism. Am J Cardiol 1996; 78:233–236


Kaye JA. A trial to evaluate the relative roles of dipyridamole and aspirin in the prevention of deep vein thrombosis in stroke patients: Boehringer Ingelheim internal report. Ingelheim, Germany: Boehringer Ingelheim, 1990
Gregory W. Albers, Pierre Amarenco, J. Donald Easton, Ralph L. Sacco and Philip Teal
Chest 2008;133;630-669
DOI 10.1378/chest.08-0720

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