Antithrombotic and Thrombolytic Therapy for Ischemic Stroke

The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy

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This chapter about treatment and prevention of stroke is part of the 7th ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence Based Guidelines. 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 Guyatt et al). Among the key recommendations in this chapter are the following: For patients with acute ischemic stroke (AIS), 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 extensive and clearly identifiable hypodensity on CT, we recommend against thrombolytic therapy (Grade 1B). For unselected patients with AIS of > 3 h but < 6 h, we suggest clinicians not use IV tPA (Grade 2A). For patients with AIS, we recommend against streptokinase (Grade 1A) and suggest clinicians not use full-dose anticoagulation with IV or subcutaneous heparins or heparinoids (Grade 2B). For patients with AIS who are not receiving thrombolysis, we recommend early aspirin therapy, 160 to 325 mg qd (Grade 1A). For AIS patients with restricted mobility, we recommend prophylactic low-dose subcutaneous heparin or low molecular weight heparins or heparinoids (Grade 1A); and for patients who have contraindications to anticoagulants, we recommend use of intermittent pneumatic compression devices or elastic stockings (Grade 1C). In patients with acute intracerebral hematoma, we recommend the initial use of intermittent pneumatic compression (Grade 1C+). 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, 50 to 325 mg qd; the combination of aspirin and extended-release dipyridamole, 25 mg/200 mg bid; or clopidogrel, 75 mg qd. In these patients, we suggest use of the combination of aspirin and extended-release dipyridamole, 25/200 mg bid, over aspirin (Grade 2A) and clopidogrel over aspirin (Grade 2B). For patients who are allergic to aspirin, we recommend clopidogrel (Grade 1C+). In patients with atrial fibrillation and a recent stroke or TIA, we recommend long-term oral anticoagulation (target international normalized ratio, 2.5; range, 2.0 to 3.0) [Grade 1A]. In patients with venous sinus thrombosis, we recommend unfractionated heparin (Grade 1B) or low molecular weight heparin (Grade 1B) over no anticoagulant therapy during the acute phase. *(CHEST 2004; 126:483S–512S)*

Key words: antithrombotic; prophylaxis; stroke; tissue plasminogen activator

Abbreviations: AIS = acute ischemic stroke; ASK = Australian Streptokinase; ATLANTIS = Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke; BI = Barthel index; CAPRIE = Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events; CAST = Chinese Acute Stroke Trial; CI = confidence interval; CVST = cerebral venous sinus thrombosis; DVT = deep venous thrombosis; ECASS = European Cooperative Acute Stroke Study; ESPS = European Stroke Prevention Study; GOS = Glasgow outcome scale; ICH = intracranial hematoma; INR = international normalized ratio; IST = International Stroke Trial; MAST-E = Multicenter Acute Stroke Trial-Europe; MAST-I = Multicenter Acute Stroke Trial-Italy; MCA = middle cerebral artery; MI = myocardial infarction; NIHSS = National Institutes of Health stroke scale; NINDS = National Institute of Neurologic Disorders and Stroke; OR = odds ratio; PE = pulmonary embolism; PFO = patent foramen ovale; PROACT = Prolyse in Acute Cerebral Thromboembolism; r-proUK = intra-arterial recombinant prourokinase; RR = relative risk; RS = Rankin scale; TIA = transient ischemic attack; TOAST = Trial of ORG 10172 in Acute Stroke Treatment; tPA = tissue plasminogen activator; TTP = thrombotic thrombocytopenia purpura; WARSS = Warfarin Aspirin Recurrent Stroke Study

I schemic stroke is a syndrome of multiple etiologies and protean clinical manifestations. Specific stroke pathogenesis and clinical features guide the optimal antithrombotic therapies for treatment or prevention (Fig 1, 2). Clinicians can identify patients at increased risk for ischemic stroke (Fig 3). 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. Approximately 20% of ischemic strokes are due to cardiogenic embolism, most commonly from atrial fibrillation. A variety of other arterial occlusive disorders may be the primary cause or variably contribute to stroke pathogenesis. Overall, approximately 30% of ischemic strokes remain cryptogenic despite a reasonably thorough evaluation. Cerebral angiography done within a few hours of cryptogenic stroke often reveals occlusions of intracranial arter-
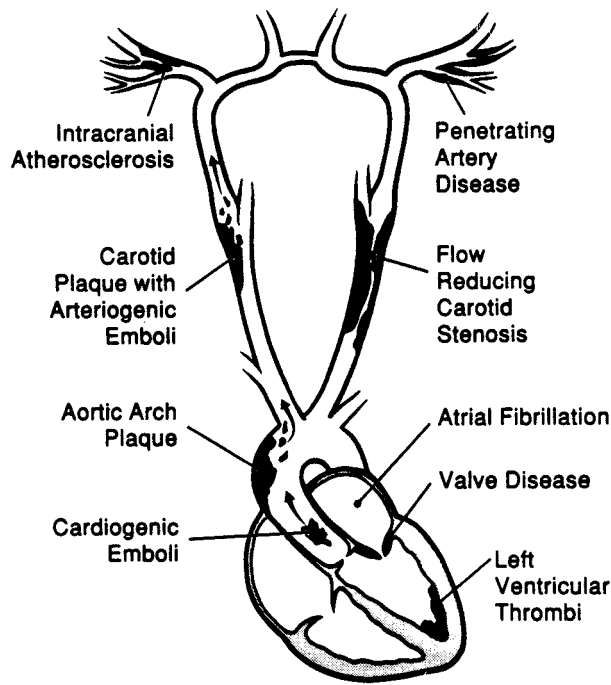
FIGURE 1. The most frequent sites of arterial and cardiac abnormalities causing ischemic stroke.

ies. 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, and determining the optimal choice of antithrombotic therapy for prevention of stroke worsening or recurrence is challenging.

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[1,3] demonstrate the presence of occlusive clot in up to 80% of
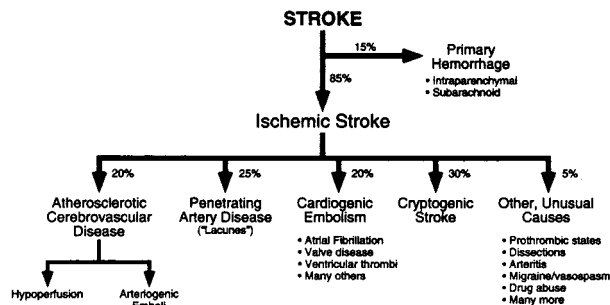

FIGURE 2. A classification of stroke by mechanism with estimates of the frequency of various categories of abnormalities. Approximately 30% of ischemic strokes are cryptogenic.
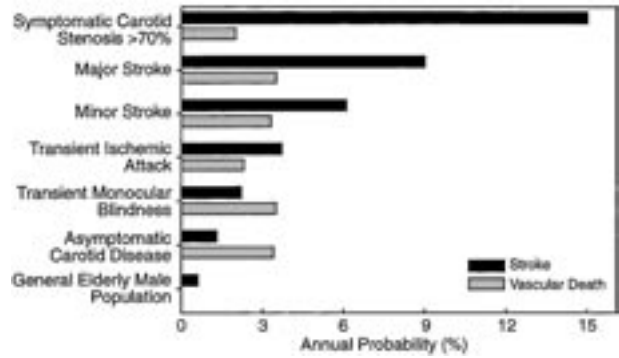

FIGURE 3. Annual risk of stroke or vascular death among patients in various high-risk subgroups.[11]

ischemic strokes. 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 that escape angiographic detection.

The therapeutic window for rescuing ischemic but still viable brain tissue is attainable for many patients but is challengingly brief. Neuronal death and brain infarction evolves 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.

Early human trials of thrombolytic therapy for ischemic stroke conducted in the pre-CT era were abandoned because of safety concerns. Available imaging technologies did not permit the exclusion of patients with intracerebral hemorrhage, tumor, or other nonischemic diagnoses, and treatment was often given days or even weeks after symptom onset.[6,7] The success of potent thrombolytic agents in the management of acute myocardial infarction (MI), a better understanding of the dynamic nature of cerebral ischemia, and the ready availability of CT imaging[8–10] rekindled interest in thrombolytic therapy for acute ischemic stroke. The 2001 American College of Chest Physicians guidelines describe the preclinical evidence and the results of early clinical trials of thrombolysis.[11]

Current status

Thrombolytic therapy for the treatment of acute ischemic stroke (AIS) has been the subject of recent intense investigation. In the past several years, nine randomized, placebo-controlled trials[12–21] have been reported using IV recombinant tissue plasminogen activator (tPA), streptokinase, or intra-arterial recombinant prourokinase (r-proUK).

Our current recommendations are based on the hierarchy of evidence drawn from meta and pooled analysis of randomized controlled trials, individual clinical trial data,

formal phase IV studies, and reports from routine clinical practice, and incorporate the accepted importance of early treatment. Cerebral infarction evolves rapidly over the first few hours of ischemic insult, and to be effective therapies must be delivered within this logistically restrictive window in order to optimize the prospects for favorable outcomes. Based on currently available data and the principle of early therapy, it is appropriate to provide recommendations based on the time to treatment (0 to 3 h, 3 to 6 h, or 0 to 6 h), the specific thrombolytic agent (tPA, streptokinase, r-proUK), and the route of delivery (IV or intra-arterial).

At present, the United States and Canada have regulatory approval sanctioning the use of tPA in stroke within 3 h of symptom onset using criteria based on the National Institute of Neurologic Disorders and Stroke (NINDS) protocol. European regulators have imposed additional inclusion/exclusion criteria for the use of tPA. The 1995 landmark report[14] from the NINDS recombinant tPA stroke study group demonstrated substantial benefit from the careful use of IV tPA in patients with AIS of < 3 h duration. This ushered in a new era in acute stroke management, requiring that stroke be recognized and treated as a time-critical emergency. Additional randomized controlled trials have helped to better define the safety, efficacy, and optimal use of thrombolytic therapy in acute stroke. Metaanalysis of thrombolytic stroke trials and pooled-data analysis of the tPA trials provides support for the use of tPA within 3 h of symptom onset. Phase IV studies[28,29] have demonstrated similar results as the NINDS trial, and reports of clinical practice experience using protocols directly derived from the NINDS trials have been generally favorable. Despite the potential benefits of this therapy, there are considerable obstacles hindering the widespread use of tPA. Thrombolytic therapy for acute stroke poses considerable logistical challenges that require a re-engineering of stroke-care systems. Table 1 describes the eligibility criteria for the studies considered in each section of the recommendations that follow.

1.1 IV tPA for AIS 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. Clinical trial data are somewhat limited in this analysis by smaller numbers and because the Cochrane metaanalysis includes not only studies that used tPA (NINDS, European Cooperative Acute Stroke Study [ECASS], and ECASS II), but also those that included patients randomized to placebo or streptokinase (Multicenter Acute Stroke Trial-Italy [MAST-I], Multicenter Acute Stroke Trial-Europe [MAST-E], and Australian Streptokinase [ASK]) within the first 3 h after symptom onset. However, the NINDS trial contributed > 50% of treated patients to this metaanalysis, and thus more than all of the other included studies combined.[22,23] The use of either thrombolytic agent 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 to 0.7; 2-sided p = 0.00002; absolute risk reduction, 13.1%). However, 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 to 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. An analysis restricted to all trials using tPA (NINDS, ECASS I, and ECASS II) as the thrombolytic agent demonstrated even more favorable results: 140 fewer dead or dependent per 1,000 tPA-treated patients (OR, 0.55; 95% CI, 0.42 to 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 three of large trials (Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke [ATLANTIS], ECASS, and NINDS) have conducted a pooled analysis[24] using original individual patient data (n = 2,775) from the six randomized controlled trials comparing IV tPA and control. An adjusted multiple logistic regression model demonstrated a relationship between onset-to-treatment time and treatment effect. Figure 4 demonstrates evidence of substantial benefit of tPA therapy delivered within the first 180 min and some benefit up to 270 min after symptom onset. The ORs for favorable 3-month outcome for patients treated with tPA (compared to placebo) were 2.8 (95% CI, 1.8 to 4.5) when tPA was administered in the first 90 min, and 1.6 (95% CI, 1.1 to 2.2) for 91 to 180 min, 1.4 (95% CI, 1.1 to 1.9) for 181 to 270 min. The lower limits of the 95% CI for the odds of a favorable outcome cross 1.0 at about 270 min, and the prospects for benefit of IV tPA therapy become small and lack significance (OR, 1.2; 95% CI, 0.9 to 1.5) for patients treated between 271 min and 360 min. The rate of important parenchymal hematoma was 5.9% with tPA (compared to 1.1% in placebo-treated patients [p < 0.01]). Symptomatic intracranial hematoma (ICH) was not significantly associated with onset-to-treatment time (p = 0.71) or baseline stroke severity (p = 0.10). This analysis[24] 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.

Large-scale trials of tPA within 3 h

Four large-scale trials using different doses, therapeutic windows, and treatment protocols have evaluated IV tPA: the NINDS recombinant tPA study,[14] ECASS I,[17] ECASS II,[21] and the ATLANTIS recombinant tPA (alteplase) acute stroke trial.[18,25] Only the NINDS recombinant tPA study exclusively included patients treated within 3 h of symptom onset.

The NINDS tPA acute stroke study group conducted a two-part, randomized, blinded, placebo-controlled study[14] that enrolled 624 patients to receive treatment within 3 h of clearly defined symptom onset. The investigators re-

Table 1—Question Definition and Eligibility Criteria for Treatment and Prevention of Stroke

| Section	Inclusion Criteria				Exclusion Criteria
	Population	Interventions or Exposure	Outcome	Methodology	
1.1.	Acute stroke (symptom onset within 3 h)	Thrombolysis with tPA	Mortality; functional status	Randomized controlled trials	
1.2.	Acute stroke (symptom onset between 3 to 6 h)	Thrombolysis with IV tPA	Mortality; functional status	Randomized controlled trials	
1.3.	Acute stroke (symptom onset within 6 h)	Thrombolysis with streptokinase	Mortality; functional status	Randomized controlled trials	
1.4.	Acute stroke (symptom onset within 6 h)	Intra-arterial thrombolysis with any agent	Mortality; functional status	Randomized controlled trials	Patients receiving thrombolysis
2.0.	Acute stroke of one of the following subtypes: large-artery atherosclerosis, progressing stroke (stroke in evolution), cardioembolic stroke, small-artery occlusion, and cryptogenic infarcts	Time (exposure)	Mortality; functional status; dependence; disability	Randomized trials and cohort studies	
2.1.	AIS not eligible for thrombolysis	Early full-dose anticoagulation	Mortality; functional status; dependence; disability	Randomized controlled trials and cohort studies	Patients receiving thrombolysis
2.2.	Ischemic stroke	Early antiplatelet therapy	Mortality; functional status	Randomized controlled trials	Patients receiving thrombolysis or full-dose anticoagulation
2.3.1.	Ischemic stroke with restricted mobility	Prophylactic low-dose subcutaneous heparin, low molecular weight heparins, or the heparinoid danaparoid	DVT by contrast venography; PE by autopsy, angiogram; symptomatic PE or DVT with a high-probability ventilation perfusion scan	Randomized controlled trials	
2.3.2.	Patients with stroke and contraindication to anticoagulation	Pneumatic compression stockings	DVT by contrast venography; PE by autopsy, angiogram; symptomatic PE or DVT with a high-probability ventilation perfusion scan	Randomized controlled trials, cohort studies	
3.1.	ICH	Early (2 d) vs delayed ($\geq$ 4 d) low-dose subcutaneous heparin	DVT by contrast venography; PE by autopsy, angiogram; symptomatic PE or DVT with a high-probability ventilation perfusion scan	Randomized controlled trials, cohort studies	
4.1.	Patients with unstable angina, MI, TIA, and nonacute stroke	Any antiplatelet agent compared with placebo or one or more other antiplatelet agents	Death; stroke or recurrent stroke; other vascular events	Randomized controlled trials	
4.2.	Patients with noncardioembolic stroke	Oral anticoagulation	Death; stroke or recurrent stroke	Randomized controlled trials	
4.3.	Patients undergoing carotid endarterectomy	Aspirin	Death; stroke or recurrent stroke	Randomized trials	
4.4.	Any patients with cardioembolic stroke or TIA	Oral anticoagulation; outcome; death or stroke	Death; recurrent stroke	Randomized trials and cohort studies	
5.0.	Any patient with CVST	Oral or parenteral anticoagulation	Death; disability	Randomized trials and cohort studies	
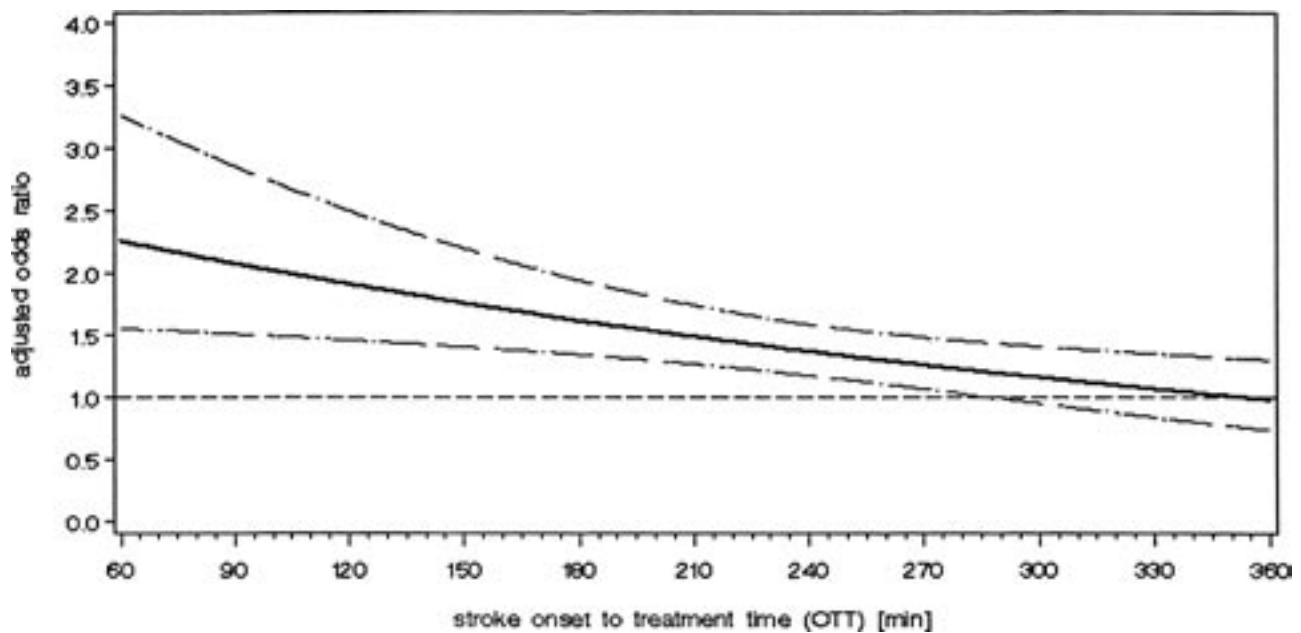
FIGURE 4. Graph of model estimating OR for favorable outcome (modified RS, 0 to 1; BI, 95 to 10; NIHSS, 0 to 1) at 3 months in recombinant tissue-type plasminogen activator (rt-PA)-treated patients compared to placebo-treated patients by time from stroke onset to treatment (onset-to-treatment time [OTT]) with 95% CIs, adjusting for age, baseline glucose level, baseline National Institutes of Health stroke scale, baseline diastolic BP, prior hypertension, and the interaction between age and baseline National Institutes of Health stroke scale. OR >1 indicates greater odds that in recombinant tissue-type plasminogen activator patients will have a favorable outcome at 3 months compared to the placebo-treated patients.[24] Reprinted with permission from Elsevier (Lancet, 2004, Vol 363, pages 768–774).

quired a pretreatment CT scan to exclude the presence of ICH, and patients had to meet a set of strict inclusion and exclusion criteria (see Recommendations). Eligible patients received IV tPA, 0.9 mg/kg (maximum of 90 mg), or placebo. The tPA was administered as a 10% bolus over 1 min, and the remainder of the total dose was infused over 60 min. In order to reduce the risk of ICH associated with hypertension, strict treatment algorithms were developed to monitor and maintain BP of < 185 mm Hg systolic and 110 mm Hg diastolic. The trial excluded patients who required aggressive measures to attain pretreatment BP below these limits.

In part 1 of the study, 291 patients were enrolled to assess early neurologic recovery. A positive early-treatment response was defined as an improvement in the National Institutes of Health Stroke Scale (NIHSS) of ≥ 4 points, or a complete neurologic recovery at 24 h after enrollment. In part 2 of the study, 2,333 patients were enrolled, and the primary outcome measure was the percentage of patients who had minimal or no disability at 3 months as measured by a global test statistic of four stroke scales (NIHSS, Barthel index [BI], modified Rankin scale [RS], Glasgow outcome scale [GOS]) and by each scale individually.

In part 1, there was no significant difference in the percentages of patients with neurologic improvement at 24 h using the criteria defined above. However, a secondary analysis showed a statistically significant improvement in the median NIHSS score at 24 h in the tPA group (8 vs 12; p < 0.02) and a significant benefit in all four outcome measures at 3 months. In part 2, the global OR for favorable outcome with tPA was 1.7 (95% CI, 1.2 to 2.6). Patients treated with tPA were at least 30% more likely to have minimal or no disability at 3 months compared with placebo-treated patients. Treatment with tPA resulted in an 11 to 13% absolute increase in the number of patients with excellent outcomes, and additional reductions were observed in the proportion of patients severely disabled or dead at 3 months. A similar degree of benefit was seen for all stroke subtypes. The mortality rate at three months was 17% in the tPA group and 21% in the placebo group (p = 0.30). Symptomatic ICH occurred in 6.4% of patients receiving tPA vs 0.6% of the placebo-treated patients (p < 0.001).

The benefits of tPA were consistent regardless of patient age, stroke subtype, stroke severity, or prior use of aspirin. While patients with severe neurologic deficits at baseline 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 demonstrated a reduction in death or severe disability with tPA compared with placebo.[26] This benefit occurred despite the increased risk of ICH in patients with severe strokes (adjusted OR, 4.3; 95% CI, 1.6 to 11.9).

There were differences in baseline NIHSS scores between tPA-treated and placebo-treated patients. These

differences increased the number of patients with favorable outcomes in the tPA group treated between 91 min and 180 min, and reduced favorable outcomes with tPA in the 0- to 90-min group. A 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-treated patients treated within the first 90 min was 2.11 (95% CI, 1.33 to 3.35), compared to 1.69 (95% CI, 1.09 to 2.62) for patients treated between 91 min and 181 min.[27] There was no onset-to-time of treatment effect on the incidence of ICH.

Phase IV studies

Two 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. Each study used standardized case report forms, and investigators strove to enroll consecutive patients.

The Standard Treatment with Alteplase to Reverse Stroke study[28] was conducted in 75 medical centers in the United States (24 academic and 33 community). A total of 389 patients were treated in a median time of 2 h and 44 min from stroke onset to treatment. The median NIHSS at baseline was 13; the mean age was 69 years. At 30 days, 35% of patients had very favorable outcomes (modified RS, 0 to 1), 43% were functionally independent (modified RS, 0 to 2), and 13% had died. The rate of symptomatic ICH was 3.3%; 7 of the 13 patients with symptomatic ICH died. Predictors of favorable outcome included a baseline NIHSS score of < 10, absence of major abnormalities on the baseline CT, age ≤ 85 years, and lower mean arterial pressures at baseline.

The Canadian Activase for Stroke Effectiveness Study[29] was conducted in 60 centers in Canada (25 academic and 35 community). A total of 1,132 patients were treated with median time to treatment of 150 min. The median NIHSS at baseline was 14, and the mean age was 70 years. At 90 days, 36% of patients had very favorable outcomes. The overall mortality rate was 21%. The rate of symptomatic ICH was 4.6%. Multivariable analysis showed that only elevated glucose (OR, 1.6; 95% CI, 1.2 to 2.3) and onset-to-treatment time (OR, 1.2; 95% CI, 1.0 to 1.5) were predictors of symptomatic ICH.

The results of these two phase IV studies demonstrate comparable safety and clinical outcomes to the NINDS trial, with a trend to lower rates of symptomatic ICH. A third study, SITS-MOST (Safe Implementation of Thrombolysis in Stroke-Monitoring Study), is in progress in Europe.

Published reports from routine clinical practice

Published reports[30–40] of the use tPA in routine clinical experience have generally been favorable, with reported rates of symptomatic ICH usually < 7%. The largest multicenter survey[40] of the use of tPA in clinical practice reported a 6% symptomatic ICH rate in 1,205 patients analyzed both retrospectively and prospectively. 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 rated of symptomatic ICH associated with protocol violations have been reported by several groups.[33,37,38,40] A survey of community experience conducted on 70 patients treated between 1997 and 1998 in 29 Cleveland area hospitals reported a symptomatic ICH rate of 15.7%; in this study,[35] 50% of patients had protocol deviations from national treatment guidelines. This exceptionally high rate of ICH underscores the need for close adherence to protocol guidelines and the importance of experience and expertise.

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 administered 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 assumes a relatively higher value on long-term functional improvement and a relatively lower value on minimizing the risk of ICH in the immediate peristroke period.

Remarks: The following criteria determine eligibility for treatment: (1) 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 ICH; and (2) exclusion criteria: minor or rapidly improving symptoms or signs, CT signs of ICH, a history of ICH, 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/μL, heparin therapy within 48 h associated with elevated activated partial thromboplastin time, clinical presentation suggesting post-MI pericarditis, pregnant or lactating women, and current use of oral anticoagulants (prothrombin time > 15 s, international normalized ratio [INR] > 1.7).

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 facili-

ties and personnel. Following tPA administration, BP should be closely monitored and kept below 180/105 mm Hg; antithrombotic agents should be avoided for 24 h.

1.1.2 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 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,[41] 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 ($p \geq 0.22$).

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.[41] Major early infarct signs on CT, defined as the presence of brain edema or mass effect, were associated with an increased risk of ICH in tPA-treated patients (OR, 7.8; 95% CI, 2.2 to 27.1).

In several other randomized trials (ECASS I, ECASS II, Prolyse in Acute Cerebral Thromboembolism [PROACT] II, ATLANTIS), patients with major early infarct changes, defined as parenchymal hypodensity $> 1/3$ of the middle cerebral artery (MCA) territory, were excluded by protocol design. 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 to 4.39). 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 data regarding the safety and efficacy of tPA in patients with major early ischemic changes on CT is insufficient.[42–45] Only 2% of the patients in the NINDS study[41] had extensive hypodensity (greater than one third of the MCA territory) on the pretreatment CT scan. As clearly identifiable and extensive hypodensity likely reflects irreversible tissue injury and a substantial increase in the risk of symptomatic ICH, we recommend against administration of thrombolytic therapy for this very small subset of patients.

Recommendation

1.1.2. For patients with extensive (greater than one third of the MCA territory) and clearly identifiable hypodensity on CT, we recommend **against** thrombolytic therapy (**Grade 1B**).

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.

1.2 IV tPA for AIS between 3 h and 6 h of symptom onset

Metaanalysis data

The Cochrane Stroke Review Group metaanalysis[22,23] reported that IV tPA administered within the first 6 h of symptom onset (n = 2,764) showed a significant (though less robust than < 3 h of 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 to 0.92; p = 0.002). The benefits with a 6-h window occurred despite the increase in symptomatic ICH from 3% in control subjects to 10% in treated patients (OR, 3.2; 95% CI; 2.4 to 4.3). A metaanalysis by Wardlaw et al[22,23] 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 to 0.96) in favor of tPA for reducing death and dependency (modified RS, 3 to 6).

Large-scale trials of t-PA within 6 h

IV tPA has been evaluated in three trials[17–19,21] randomizing patients as late as 6 h after symptom onset, the majority of whom were treated between 3 h and 6 h The ECASS I trial[17] was a multicenter, blinded, placebo-controlled trial that randomized 620 patients within 6 h of stroke onset to treatment with IV tPA at a dose of 1.1 mg/kg (maximum of 100 mg) or placebo. Primary end points included the BI and modified RS at 90 days. Patients with major early infarct signs affecting $> 33\%$ of the MCA territory were to be excluded, as were patients with clinically very severe strokes. An intention-to-treat analysis and a target population analysis were planned a priori in the protocol. The target population analysis included only 511 patients because 109 patients were

eliminated due to major protocol violations, most commonly involving violation of the CT exclusion criteria for early infarct signs.

There was no significant difference in the BI at 3 months in either the intention-to-treat or target population (patients without protocol violations). In the target population analysis, there was a significant difference of 1 point in the RS, favoring treatment with tPA (p = 0.035). In the target population, 41% of tPA-treated patients were asymptomatic or had minimal disability compared with 29% in the placebo group (RS, 0 or 1; p < 0.05). Other predefined secondary end points, including the combined BI and RS, speed of neurologic recovery, and length of hospital stay, favored tPA-treated patients.

There were no statistically significant differences in the 30-day mortality rates or in the overall incidence of ICH. However, the incidence of major parenchymal hemorrhages was 19.8% in the tPA group vs 6.5% in the control group (p < 0.001). A *post hoc* exploratory analysis of the ECASS data showed that the severity of the initial clinical deficit (OR, 2.5; 95% CI, 1.6 to 4.0) and the presence of early major ischemic changes (hypoattenuation exceeding one third of the MCA territory or diffuse swelling of the entire hemisphere) on CT scan were associated with increased risk of hemorrhagic infarction (OR, 3.5; 95% CI, 2.3 to 5.3). The ECASS investigators concluded that tPA might be effective when administered within 6 h of stroke onset, provided there are no major signs of infarction on the pretreatment CT scan.

Differences between the ECASS I trials and NINDS include the treatment window (6 h vs 3 h), the dose of tPA (1.1 mg/kg vs 0.9 mg/kg), and the rigid BP parameters dictated by the NINDS protocol. In NINDS, half of the patients (> 300) were enrolled in < 90 min from symptom onset. In ECASS I, the median time to treatment was 4.3 h; only 92 patients were enrolled within 3 h of stroke onset.

The ECASS II trial[21] was designed to test the same dose of tPA (alteplase) used in the NINDS trial (0.9 mg/kg with a maximum total dose of 90 mg) but with a 6-h treatment window. A total of 800 patients were randomized in to IV tPA (n = 409) or placebo (n = 391). Concomitant antithrombotic agents were prohibited during the first 24 h except for low-dose subcutaneous heparin. BP parameters were carefully controlled as in the NINDS trial. Investigators had to successfully complete a standardized CT training program.

The primary end point was the modified RS at 90 days, dichotomized as a favorable outcome (modified RS of 0 or 1) or unfavorable (modified RS of 2 to 6). In the intention-to-treat analysis, 40.3% (n = 165) of tPA-treated patients had a favorable outcome vs 36.3% (n = 143) placebo group patients (absolute difference, 3.7%; p = 0.28). A *post hoc* analysis of modified RS scores dichotomized for independence (favorable modified RS of 0, 1, 2) or death and dependency (modified RS of 3 to 6) showed favorable outcomes in 54.3% (n = 222) treated with tPA, vs 46% (n = 180) in the placebo-group patients (absolute difference, 8.3%; p = 0.024). There were no differences in the death rates: 10.3% with tPA and 10.5% with placebo.

Symptomatic ICH occurred in 8.8% of the tPA-treated patients vs 3.4% in placebo-treated patients.

The differences in efficacy between NINDS trial and ECASS II may be explained by differences in the patient populations and the treatment window. ECASS II patients had milder strokes on average than the NINDS trial patients. The median baseline NIHSS scores in ECASS II were 11 in both groups vs 14 and 15 for tPA and placebo, respectively, in NINDS. In ECASS II, only 158 patients received study drug within 3 h of symptom onset. In the NINDS trial, patients were treated in < 3 h, with half of the patients receiving treatment in < 90 min.

The ATLANTIS trial[19] was initiated in 1991 to evaluate the safety and efficacy of IV recombinant tPA in patients with ischemic stroke of < 6 h duration (part A). In 1993, the study was changed to 0 to 5 h (part B) due to safety concerns in the 5- to 6-h group. In 1996, following the US Food and Drug Administration approval of tPA in the first 3 h, part B was modified to a 3- to 5-h window.[18] The protocol was similar to the NINDS study except for the time windows. A total of 142 patients were randomized in part A, and a total of 613 patients were randomized on an intent-to-treat basis in part B. The analysis of the target population was based on the 547 patients in part B who were actually treated within the 3- to 5-h window. The trial was terminated in July 1998 after an interim analysis suggested that detection of a beneficial effect of tPA was highly unlikely. In the target population, 32% of placebo-treated patients and 34% of tPA-treated patients had an excellent recovery at 3 months (p = 0.65). The rate of symptomatic ICH was 1.1% with placebo vs 7.0% with tPA (p = 0.001). The 90-day mortality rate was 6.9% with placebo and 11.0% with tPA. Intention-to-treat analysis yielded similar results. The investigators concluded that the use of tPA beyond 3 h was not supported by this study. In ATLANTIS, the median time to treatment with tPA was 4 h and 35 min and the mean baseline NIHSS was 11. In comparison to the NINDS study, the patients in ATLANTIS had milder strokes on average and were treated quite late. See Table 2 for a comparison of the key outcomes of NINDS, ECASS I, ECASS II, and ATLANTIS B.

Recommendation

1.2. For unselected patients with AIS of > 3 h but < 6 h, we suggest clinicians **not** use IV tPA (**Grade 2A**).

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 ICH and death, and a relatively high degree of risk aversion.

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.

Table 2—*Randomized Placebo-Controlled Trials of IV tPA in AIS**

Trials	Patients, No.	Dose, mg/kg (Maximum)	Treatment Window, h	Symptomatic ICH, %		Death tPA	Death Placebo	Good Outcome	
				tPA	Placebo			tPA	Placebo
NINDS[14]	624	0.9 (90)	< 3	Study	0.6†	17.4	20.6	39†	26†
ECASS I[17]	620	1.1 (100)	≤ 6	19.8†	6.5†	22	15.6	41	29
ECASS II[21]	800	0.9 (90)	≤ 6	8.8†	3.4†	10.5	10.7	40.3	36.3
Atlantis A[18] (0–6 h)	142	0.9 (90)	≤ 6	11.3†	0†	22.5†	7†	47	49
Atlantis B[25] (3–5 h)	547	0.9 (90)	3–5	7.0†	1.1†	11	6.9	34	32

*Data are presented as No. unless otherwise indicated.
†Statistically significant.

1.3 IV streptokinase for AIS between 0 h 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 streptokinase vs control treatment trials (OR, 5.20; 95% CI, 3.25 to 8.32). There was no effect on death or dependency at the end of follow-up for either streptokinase without aspirin vs control (OR, 0.94; 95% CI, 0.72 to 1.24) or streptokinase plus aspirin vs aspirin (OR, 1.09; 95% CI, 0.69 to 1.73).[22,23]

Pooled data analysis

An analysis[46] of individual patient data pooled from the 1,292 patients in the ASK, MAST-I, and MAST-E trials showed that treatment with streptokinase was associated with a significantly increase risk of death at 10 days (relative risk [RR], 1.94; 95% CI, 1.55 to 2.42; p < 0.001) and 3 months (RR, 1.46; 95% CI, 1.24 to 1.73; p < 0.001). There was no difference between streptokinase-treated and patients for death or dependency at 3 months (RR, 0.99; 95% CI, 0.92 to 1.06; p = 0.72). Treatment with streptokinase was associated with significantly more hemorrhagic transformations (RR, 1.85; 95% CI, 1.58 to 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 to 1.05).[46]

The streptokinase trials and subsequent meta 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 streptokinase is administered during a 6-h window after symptom onset. Patients given a combination of streptokinase and aspirin had the worst outcomes.

Individual trials

Three placebo-controlled trials of IV streptokinase for acute stroke—MAST-I, MAST-E, and ASK trial—were initiated but stopped prematurely by safety committees due to the unfavorable rate of early mortality and intracranial bleeding associated with streptokinase.[12,13,15]

The MAST-I study[13] was stopped after 622 patients were randomized to treatment within 6 h of stroke symptom onset. Treatment consisted of 1.5 million U of IV streptokinase administered over 1 h, 300 mg/d of aspirin for 10 days, both drugs, or control.[13] The 10-day mortality rate was significantly higher in the streptokinase groups (27% vs 12%; OR, 2.7; 95% CI, 1.7 to 4.4) and was highest (34%) in patients who received both streptokinase and aspirin. The early mortality rate with streptokinase alone was 19%, compared with 13% in the placebo group. The rate of symptomatic ICH was 6% in streptokinase-treated patients, 10% in those who received combined therapy, 2% receiving aspirin alone, and 0.6% in the control group. There was a nonsignificant reduction in death and disability at 6 months in patients treated with streptokinase.

The MAST-E study[15] was suspended by the safety committee after 270 patients with stroke of < 6 h duration were enrolled. Patients were treated with 1.5 million U of streptokinase or placebo. Symptomatic ICH occurred in 17.5% of patients in the streptokinase group and 3.0% of the placebo group. The 10-day mortality rates were 35% with streptokinase vs 18% with placebo. There was no reduction in death or dependency at the end of follow-up.

The ASK trial[12] randomized 340 patients within 4 h of stroke onset to receive either 1.5 million U of streptokinase over 1 h or placebo. This trial was abandoned because of an increase in mortality and disability in the streptokinase-treated group, particularly in patients treated > 3 h after symptom onset. There was a trend toward improved outcomes in patients treated within the first 3 h.

Recommendation

1.3. For patients with AIS, we recommend **against** streptokinase (**Grade 1A**).

1.4 Intra-arterial thrombolysis for AIS

Intra-arterial thrombolysis

Intra-arterial 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 Prolyse in Acute Cerebral Thromboembolism (PROACT) I and II showed a barely significant reduction in death and disability with intra-arterial r-proUK initiated within 6 h of symptom onset in patients with MCA occlusion (OR, 0.55; 95% CI, 0.31 to 1.00). There was a trend toward increased risk of symptomatic ICH (OR, 2.39; 95% CI, 0.88 to 8.47) and a weak trend for reduced all cause mortality associated with the use of r-proUK.

Individual trial results

Two randomized trials[16,20] comparing intraarterial r-proUK plus IV heparin vs IV heparin have been conducted in patients with occlusion of the MCA (M1 or M2) of < 6 h in duration. The PROACT I trial[16] treated 40 patients with MCA occlusions with either intra-arterial r-proUK (n = 26) or placebo (n = 14). 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 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 r-proUK (58%) than with placebo (14%; 2-sided p = 0.017). There was nonsignificant difference in the rate of early symptomatic hemorrhagic transformation, which occurred in 15.4% of the r-proUK 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 r-proUK but did not reach statistical significance. Recanalization rates and the risk of brain hemorrhage were influenced by the dose of heparin.

The PROACT II study[20] was designed to further test the efficacy and safety of intra-arterial r-proUK in patients with MCA of < 6 h in duration. More than 12,000 patients were evaluated for inclusion in the trial, and 474 patients underwent a screening conventional cerebral angiogram. A total of 180 patients had angiogram-confirmed MCA occlusions and were randomized to receive 9 mg of intra-arterial r-proUK 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 r-proUK in the primary outcome analysis, with 40% of treated patients recovering to a modified RS of ≤ 2 compared with 25% of control patients (absolute risk reduction, 15%; p = 0.043; relative risk reduction, 60%). Mortality was 25% in the r-proUK study arm and 27% in the control group. Symptomatic ICH occurred in 10% of r-proUK patients and 2% of control patients (p = 0.063). The recanalization rate (Thrombolysis in Myocardial Infarction 2 or 3) was 66%

for r-proUK 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 intra-arterial treatment was 5.3 h. Mechanical clot disruption was not permitted. Benefits of r-proUK were greatest in patients with baseline NIHSS scores of 11 to 20.

Published reports of intra-arterial therapy in clinical practice

r-proUK is not available for routine clinical use. Reports[47–58] of intra-arterial thrombolysis using tPA or urokinase in selected patients have generally showed favorable results, or better than anticipated clinical outcomes, despite increases in the rate of symptomatic ICH. Treatment times have been beyond 3 h in most cases, and patients often had severe stroke syndromes due to large-vessel occlusions. Symptomatic ICH was more frequent with intra-arterial thrombolysis (9.5% vs 3%, p = 0.046).

The natural history of acute basilar artery occlusion is grim with mortality rates as high as 80 to 90% and the few survivors tend to be severely disabled. Several case series[49,55,57,59–64] have reported outcomes that appear to be more favorable than expected with intra-arterial thrombolysis in patients with acute basilar occlusion. 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 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 intra-arterial therapy will be conducted in patients with basilar occlusion, as many stroke centers accept intra-arterial thrombolysis as standard care for this condition and would likely refuse to randomize patients to a control group.

Recommendations

1.4.1. For patients with angiographically demonstrated MCA occlusion and no signs of major early infarction on the baseline CT scan, who can be treated within 6 h of symptom onset, we suggest intra-arterial thrombolytic therapy with tPA (**Grade 2C**).

1.4.2. For patients with acute basilar artery thrombosis and without major CT/MRI evidence of infarction, we suggest intra-arterial thrombolysis with tPA (**Grade 2C**).

Remarks: Intra-arterial thrombolytic therapy has not received regulatory approval for stroke treatment. Intra-arterial therapy requires expertise in stroke management and a trained neurointerventionalist. Treatment should be limited to clinical trials or to carefully selected patients

after informed consent. Intra-arterial therapy should be considered only when there are adequate personnel and facilities to ensure appropriate patient selection, and procedural and postprocedural care. 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 determined by case-specific variables. Good clinical results in individual patients have been reported beyond 6 h. Clinical trials are in progress evaluating the use of combined IV and intra-arterial tPA. Several novel catheter devises designed to expedite clot lysis are under investigation.

1.5 Use of MRI

The use of MRI rather than CT for selection of patients for thrombolytic therapy is under investigation and appears to be very promising although logistical access issues have limited widespread use. Preliminary data suggest that specific MRI profiles may identify patients who are particularly likely to benefit from thrombolytic therapy.[65–67] New MRI techniques including perfusion-weighted and diffusion-weighted may detect ischemic injury in the first hour and may reveal the extent of reversible and irreversible injury.[68] In addition, MRI appears to be highly sensitive for identification of acute brain hemorrhage.[68–70]

2.0. AIS: Patients not Eligible for Thrombolysis

For patients with acute cerebral infarction who are not eligible for IV or intra-arterial 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 have not been adequately evaluated in the acute setting. The rationale for the use of antithrombotic therapy for treatment of AIS 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 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.[71] In the North American Symptomatic Carotid Endarterectomy Trial,[72] 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[73] 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.[73] Moreover, recurrent stroke risks from natural history studies are generally greater than those observed in the control groups of randomized trials that reported risks of 0.6 to 2.2% per week.[74]

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*) has frequently been considered an indication for anticoagulation, although supportive randomized clinical trial data are scant. Studies[75–79] 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. Many of these studies, however, were not randomized or blinded, had poorly defined inclusion and exclusion criteria, and did not use standardized assessments for outcomes.[80] Other nonrandomized studies[81–83] of consecutive patients with unstable stroke who received IV heparin have shown high rates (27 to 50%) of further progression despite treatment.

For cardioembolic strokes, older studies[104,105] suggested a recurrence risk that approached 1% per day in the first 14 days; however, more current studies[71,84,85] 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[85] 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.[86] Strokes related to atrial fibrillation, however, are often major and associated with significant disability.[87]

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).[88] The underlying mechanism

in the majority of lacunar strokes arises from small-vessel disease, usually caused by lipohyalinosis.[89] 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.[89]

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. Results of CT or MRI scanning 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.[90] 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.[91–95] There are no data to indicate that the 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[96] showed that immediate anticoagulation of patients with AIS was **not** associated with a significant reduction in death or dependency.

Individual trials

Randomized trials using unfractionated heparin, low molecular weight heparins, and heparinoids have helped clarify the benefits and risks of anticoagulants for treatment of AIS. 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 fixed doses to adjusted doses of these agents.

Despite the clinical use of full-dose IV unfractionated heparin, only a single randomized trial[97] 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).[97] 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.

Subcutaneous administration of heparin was evaluated in the International Stroke Trial (IST).[98] In this unblinded mega-trial,[98] 19,435 patients with suspected AIS from 467 hospitals in 36 countries were randomized within 48 h of onset (median, 19 h) to aspirin, subcutaneous heparin, both, or neither in a factorial design. Half were allocated 300 mg of aspirin and half "avoid aspirin"; half were allocated unfractionated heparin, administered subcutaneously, 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 up 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[98] 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 AIS, 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. As shown in Figure 4, 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 the IST[98] suggest that the use of early unmonitored subcutaneous 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 antifactor Xa to antifactor 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 AIS with mixed results. In the Hong Kong trial,[99] the nadroparin-treated patients had better 6-month outcomes. In this trial,[99] 308 patients were randomized to three groups (high-dose 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[100] completed in Europe, Canada, and Australia (the Fraxiparine in Ischemic Stroke Study) was unable to corroborate these beneficial effects. In this trial,[100] 767 AIS 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 group, 57.2% for the low-dose group, and 56.8% for the placebo groups.[100]

The Trial of ORG 10172 in Acute Stroke Treatment (TOAST)[101] evaluated the low molecular weight heparinoid danaparoid (ORG 10172) among 1,281 patients with ischemic stroke treated within 24 h of onset. In this multicenter, blinded, placebo-controlled trial,[101] patients were treated for 7 days with an IV infusion of the heparinoid, and daily dose adjustments were based on antifactor Xa units. 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. 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%; Fig 5). 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.% vs 27.8%; $p = 0.01$). There was no significant reduction in

FIGURE 5. Three-month outcomes in the TOAST trial.[101] Overall, patients treated with the heparinoid danaparoid were no more likely to have a favorable outcome than placebo-treated patients. Subgroup analysis revealed an apparent benefit among patients with stroke caused by large-artery atherosclerosis.

stroke progression, 7-day mortality, or the risk of stroke recurrence or systemic embolic events. In a predefined subgroup analysis from TOAST,[101] patients with large-artery atherosclerotic stroke revealed a benefit in favorable outcome from danaparoid at 3 months (68.1% 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; however, this finding should be verified in additional studies.[101]

Other studies using different low molecular weight heparin agents with fixed subcutaneous doses have also been completed. Tinzaparin was evaluated in a blinded, randomized, aspirin-controlled trial of patients with AIS treated within 48 h.[102] 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.[103] No dose-dependent difference was observed in efficacy, and bleeding was greater in the higher-dose group.

Cardioembolic stroke

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.[104–106] 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 (2 of 20 patients) in those who did not receive anticoagulants.

The use of heparin for acute cardioembolic stroke has been challenged by the lack of efficacy of both unfractionated subcutaneous heparin in the subgroup with atrial fibrillation in the IST, and heparinoid in the cardioembolic subgroup in the TOAST trial.[101] Low molecular weight heparin was evaluated in the Heparin in Acute Embolic Stroke Trial.[85] In this study, 449 patients with atrial fibrillation and AIS (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 bid subcutaneously). 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 difference 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%, $p = 0.028$).
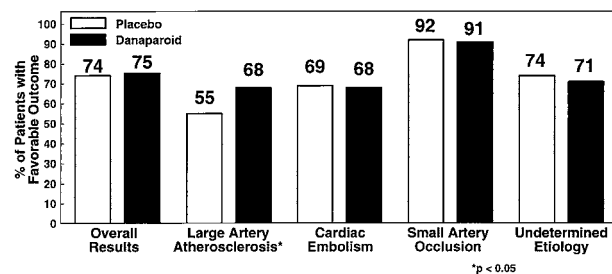
Limitations of available data

There is still debate regarding the appropriate use of heparin and low molecular weight heparins for treatment of acute stroke, although more recent reviews[74,107–109] have strongly discouraged their indiscriminant use. 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.[110] A large infarct size, judged by neuroimaging findings or the clinical syndrome, and elevated BPs are predictors of a greater risk of hemorrhagic transformation.[105] The risk is also greater among those treated with larger doses of anticoagulation.[111]

Some limitations of clinical trials of anticoagulants for stroke treatment include a much 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) 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, trials[110] 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. There is inadequate randomized clinical trial data on full-dose unfractionated IV heparin in acute stroke. Questions remain regarding the efficacy of heparin for treatment of progressing stroke, the role of immediate anticoagulation for atherosclerotic stroke, and the risk-benefit ratio for acute cardioembolic stroke. Although the results of recent trials are not supportive of the efficacy of anticoagulation, there are some continuing efforts to improve trial designs and produce more definitive results among hyperacute stroke patients, such as in the Rapid Anticoagulation Prevents Ischemic Damage trial.[112,113] Based on the current data, however, recent guidelines from the American Heart Association and the American Academy of Neurology have not supported the use of anticoagulation in acute ischemic stroke to alter outcome other than for DVT prophylaxis.[114]

Recommendation

2.1. For patients with AIS, we suggest clinicians **not** use full-dose anticoagulation with IV, subcutaneous, or low molecular weight heparins or heparinoids (**Grade 2B**).

Remarks: Some experts recommend early anticoagulation for various specific stroke subgroups including cardioembolic stroke, progressing stroke, stroke due to large-artery atherosclerotic stenosis, documented intra-luminal thrombus, or arterial dissections. Clinical trials have not, however, adequately evaluated adjusted-dose IV anticoagulation in these selected stroke patients. No trials have evaluated the role of very early anticoagulation (< 12 h after stroke onset) in any stroke population.

2.2 Antiplatelet agents for altering outcomes in acute stroke in patients not eligible for thrombolysis

Metaanalysis

A metaanalysis[115] from 41,325 subjects enrolled in eight trials evaluated the efficacy of antiplatelet agents. For every 1,000 acute strokes treated with aspirin, approximately 7 fewer early recurrent ischemic strokes were observed and 13 fewer patients will be dead or dependent at 6 months at the expense of two or more ICHs. These overall absolute benefits may be small, but they are significant, and given the relative safety and low cost of aspirin represent important public health measures to improve stroke outcomes.

Individual trials

Aspirin is the only antiplatelet agent that has been evaluated for the treatment of AIS. Other antiplatelet agents such as ticlopidine, clopidogrel, or extended-release dipyridamole plus aspirin have not been evaluated in the setting of AIS. Data on aspirin are available from two mega-trials, IST[98] and the Chinese Acute Stroke Trial (CAST).[116] 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.[98,116] 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,[116] 21,106 patients with AIS 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 demonstrate that the use of aspirin in the treatment of AIS is safe and produces a small but definite net benefit.

Recommendation

2.2. For patients with ischemic stroke who are not receiving thrombolysis, we recommend early aspirin therapy, 160 to 325 mg/d (**Grade 1A**).

Remarks: Aspirin should be started within 48 h of stroke onset, and may be used safely in combination with low doses of subcutaneous heparin for DVT prophylaxis. Aspirin is contraindicated among those with aspirin allergy or those with active GI bleeding.

2.3 Antithrombotic therapy for prevention of DVT and PE in AIS

DVT and PE are frequent complications of stroke, with approximately 5% of early deaths attributed to PE.[117] Large trials (see chapter in this Supplement on the Prevention of Venous Thromboembolism) 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 approximately 60%. For acute stroke patients, few randomized trials have individually been able to demonstrate a significant decrement in the risk of these complications. An overview analysis[118] in 1993 reviewed the results of 10 trials that evaluated heparin in 1,047 patients with AIS, and found an 80% reduction in DVT and a 58% reduction in PE. In the IST,[98] there was a significant reduction in the frequency of fatal or nonfatal PE, from 0.8 to 0.5%, among those treated with subcutaneous unfractionated heparin ($p < 0.05$). 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 unfractionated heparin in preventing DVT (see chapter on Prevention of Venous Thromboembolism in this Supplement) In the TOAST study, DVTs were significantly reduced in the heparinoid-treated group compared with the placebo group. In a systematic review[119] of 10 low molecular weight heparin trials, the risk of DVT and PE were significantly lowered at the expense of an increased risk of significant bleeding. In another systematic review,[114] low molecular weight heparin was significantly superior to standard unfractionated heparin; however the number of pulmonary emboli, deaths, ICH, or extracranial hemorrhage were too small to detect a precise difference.

DVT and PE prophylaxis are essential reasons to consider early low-dose anticoagulant therapy in acute stroke patients.[120,121] For patients with contraindications to anticoagulants, intermittent pneumatic compression devices or elastic stockings are recommended (see chapter on Prevention of Venous Thromboembolism).

Recommendations

2.3.1. For acute stroke patients with restricted mobility, we recommend prophylactic low-dose subcutaneous heparin or low molecular weight heparins or heparinoids (**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 intermittent pneumatic compression devices or elastic stockings (**Grade 1C**).

3.0 DVT/PE prophylaxis in patients with ICH

3.1 Heparin for DVT/PE prophylaxis in patients with ICH

Only one small study[122] is available to address the risk of early prophylactic therapy with anticoagulants in patients with ICH. In this study, 22 patients with spontaneous ICH were treated with subcutaneous heparin beginning on the second day after the ICH. When compared with historical control subjects, early (day 2) low-dose heparin (5,000 U tid of subcutaneous heparin-sodium) significantly lowered the incidence of PE compared with delayed (day 4 or day 10) heparin therapy. No increase in the number of patients with rebleeding in the brain was observed. These results suggest that the early use of low-dose heparin may be safe and effective in ICH patients.

Recommendation

3.1. In patients with an acute ICH, we recommend the initial use intermittent pneumatic compression (**Grade 1C+**) for the prevention of DVT and PE. In stable patients, we suggest low-dose subcutaneous heparin may be initiated as soon as the second day after the onset of the hemorrhage (**Grade 2C**).

Underlying values and preferences: the recommendation for subcutaneous heparin assumes a relatively low degree of risk aversion.

4.0 Stroke Prevention

The Antithrombotic Trialists' metaanalysis

Platelet antiaggregation drugs prevent strokes. Aspirin is the most widely studied antiplatelet drug and, until recently, it was the only drug used broadly for this purpose. Now, clinical trial results indicate that ticlopidine and clopidogrel are also effective for prevention of stroke and other vascular events in patients with cerebrovascular disease. Dipyridamole (particularly when combined with aspirin) also is effective for prevention of stroke. The selection of individual agents is primarily based on interpretation of their relative efficacy, safety, and cost.

The Antiplatelet Trialists[117]conducted a metaanalysis that assessed the effect of antiplatelet drugs in patients with various manifestations of atherosclerosis. An update[123] of their metaanalysis was published in 2002 and included studies published prior to September 1997. The Antiplatelet Trialists also changed their name to the Antithrombotic Trialists. This latest analysis[123] included 144,051 patients with previous MI, acute MI, 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, MI, or vascular death. This outcome cluster includes hemorrhagic stroke and death due to hemorrhage. They also analyzed nonfatal stroke, nonfatal MI, 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 agents reduce the odds of the composite outcome of stroke, MI, or vascular death in secondary prevention by approximately 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 MI by approximately 34%, and vascular mortality by 15%.

The Antithrombotic Trialists also analyzed the differences in the response of patients > 65 and < 65 years of age, 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 agents on prevention of strokes, MIs and vascular deaths is the same in patients entering studies because of prior stroke/TIA as it is for patients entering because of prior MI or other vascular disorders. The Antithrombotic Trialists found that whereas all antiplatelet agents reduced the odds of stroke, MI, 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[124] 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, MI, or vascular death by only 16%. When this odds reduction is converted to the more conventional relative risk reduction, 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 MIs. 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, MI, 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.[125] The focus on the composite cluster also is important because stroke and TIA patients often die of MI or other vascular causes as well recurrent stroke.[126–128]

4.1 Prevention of cerebral ischemic events in patients with noncardioembolic TIA or stroke: antiplatelet drugs versus placebo or versus an alternative antiplatelet drug

Aspirin

The Swedish Aspirin Low-Dose Trial[129] compared aspirin, 75 mg/d, with placebo in 1,360 patients with minor stroke/TIA. The 18% relative risk reduction in stroke plus all death in the aspirin-treated group was statistically significant (p = 0.02). The relative risk reduction in stroke, MI, 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[124] found for all doses of aspirin in similar patients.

The Dutch TIA Trial[130] compared two dosage regimens of aspirin, 30 mg/d vs 283 mg/d, in 3,131 patients with minor stroke/TIA. The primary outcome measure was stroke, MI, or vascular death. The investigators found that 30 mg/d of aspirin 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[131] and the Algra and van Gijn metaanalysis,[124] 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[132] (see below) reported that 50 mg per day 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 United States Food and Drug Administration (FDA) published their new recommendation that 50–325 mg of aspirin daily be used for prevention of ischemic stroke.[133]

One additional direct comparison of low and high aspirin doses was recently studied in patients undergoing carotid endarterectomy (the ASA and Carotid Endarterectomy [ACE] trial).[134] ACE compared, head-to-head, aspirin at low doses (81 or 325 mg daily) vs high doses (650 or 1300 mg daily) in 2,804 patients treated for a total of 3 months. There were no significant differences between low and high doses for any endpoint at 30 days, or for the endpoints stroke and death, and ipsilateral stroke and death at 3 months. Patients who received low-dose aspirin had a significantly lower rate of stroke, MI, and death at three 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.

Data from numerous trials establish that aspirin reduces the risk of stroke, MI, and vascular death in a wide variety of patients who are at high risk for these atherothrombotic outcomes.

Ticlopidine

Ticlopidine hydrochloride is a thienopyridine that inhibits adenosine diphosphate-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.[135,136]

The Ticlopidine Aspirin Stroke Study (TASS)[91] enrolled 3,069 patients who presented within 3 months 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% relative risk reduction for stroke compared with aspirin, and a 9% reduction in the endpoint cluster of stroke, MI, or vascular death at 3 years (intention-to-treat analysis).[137]

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. Bleeding from other anatomic sites was infrequent and about equal in the two treatment groups. 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, blood counts are required at 2-week intervals for the first 3 months of ticlopidine therapy, *ie*, six blood counts in 3 months.

The Canadian American Ticlopidine Study (CATS)[136] involved 1,072 patients who were enrolled after the occurrence of a major ischemic stroke. 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, MI, or vascular death of 15.3% per year, demonstrating the seriousness of stroke as a predictor of subsequent vascular events. Ticlopidine reduced the relative risk of stroke, MI, or vascular death by 30%, to 10.8% (p = 0.006), in the on-treatment analysis. The same outcome cluster was reduced by 23% (p = 0.020) in the ticlopidine group using the intent-to-treat approach. Adverse effects were similar to those noted in TASS. Ticlopidine reduced the relative risk of ischemic stroke by 33.5% (p = 0.008) in the on-treatment analysis.

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.[138] This study did not demonstrate any benefit of ticlopidine over aspirin for stroke prevention.

Taken together, these trials show that ticlopidine reduces the risk of stroke and other vascular outcomes in patients with cerebrovascular disease. The two randomized studies that compared ticlopidine with aspirin in stroke or TIA patients produced conflicting results regarding whether ticlopidine is more effective than aspirin. Ticlopidine is associated with an approximately 1% incidence of severe neutropenia and > 60 cases of ticlopidine-associated thrombotic thrombocytopenia purpura (TTP) have been reported.[139,140]

Clopidogrel

Clopidogrel is a thienopyridine derivative of the same chemical family as ticlopidine. It is a potent inhibitor of platelet aggregation induced by adenosine diphosphate. Its antithrombotic effects were evaluated in the Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study.[141] The CAPRIE study was a randomized, blinded, multicenter trial designed to assess the relative efficacy of clopidogrel (75 mg per day) and aspirin (325 mg per day) in reducing the risk of the composite outcome of ischemic stroke, MI, or vascular death, and to determine their relative safety. Three groups of patients were studied; those with recent ischemic stroke, recent MI, 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, MI, or vascular death, vs 5.83% with aspirin, for a relative risk reduction of 8.7% in favor of clopidogrel (95% CI; 0.3 to 16.5; p = 0.043), and an absolute risk reduction of 0.5%. The corresponding on-treatment analysis showed a relative risk reduction of 9.4%. When serious hemorrhages were considered along with the primary outcome cluster in an intent-to-treat analysis the relative risk reduction with clopidogrel was 9.5% (95% CI; 1.2 to 18.5). Finally, when the results in the CAPRIE study are analyzed using the Antithrombotic Trialists' technique (*ie*, intent-to-treat; all stroke, MI, or vascular death, including hemorrhagic) and by odds reduction, there is a reduction of 10% favoring clopidogrel.

For the 6,431 patients entered into the CAPRIE study with a stroke as the qualifying condition, the relative risk reduction for ischemic stroke, MI, or vascular death was 7.3% (95% CI, 5.7 to 18.7; p = 0.26), and the relative risk reduction for the endpoint 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%). There were 10 patients in the clopidogrel group (0.10%) with significant reductions in neutrophils to < 1,200/mm^3, compared with 16 patients in the aspirin group (0.17%). The numbers of patients with severe neutropenia (< 450/mm^3) were 5 and 4 in the clopidogrel and aspirin groups, respectively. The overall safety profile of clopidogrel is similar to that of 325 mg per day of aspirin. A recent report identified 11 cases of TTP associated with clopidogrel among the > 3 million patients who have received this agent.[139] Ten of these 11 cases occurred within 2 weeks of initiation of clopidogrel, and most responded favorably to plasma exchange, although 2 patients required 20 or more exchanges before clinical improvement. No cases of TTP were observed in > 30,000 patients studied in clinical trials.[141,142]

The CAPRIE study data indicate that clopidogrel is more effective than aspirin in reducing the combined risk of ischemic stroke, MI, or vascular death in patients with atherosclerotic vascular disease. No statistically significant benefit over aspirin was seen for the stroke patients entered in this study.

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. This study of 12,562 randomized patients found that the clopidogrel plus aspirin group showed a 20% relative risk reduction 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.

Results of the Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischemic Attack of Ischemic Stroke (MATCH) study were recently presented. In this trial, 7,599 patients with a recent stroke or TIA were randomized to receive clopidogrel (75 mg per day) vs clopidogrel (75 mg per day) plus low dose aspirin (75 mg per day). During an 18 month follow-up period there was no statistically significant dif-

ference in the rate of ischemic events (stroke or MI) between the treatment groups, however, in the patients treated with the combination of clopidogrel and aspirin there was a statistically significant increase in life threatening bleeding (2.6% vs 1.3%). Intracranial hemorrhage occurred in 25 patients in the clopidogrel group vs 40 in the combination therapy group.

Dipyridamole

The Antithrombotic Trialists[117] analyzed all trials involving dipyridamole alone vs placebo and dipyridamole combined with aspirin vs placebo, including the European Stroke Prevention Study (ESPS)-2, which used an extended-release formulation of dipyridamole. Fifteen trials compared dipyridamole alone vs placebo and showed a 16% odds reduction for stroke, MI, or vascular death favoring dipyridamole. Forty-six trials compared dipyridamole combined with aspirin vs placebo and showed a 30% odds reduction in stroke, MI, or vascular death favoring the combination.

Twenty-five trials compared the combination of dipyridamole plus aspirin vs aspirin alone for prevention of the composite outcome of stroke, MI, or vascular death. The odds reduction for all vascular events was 6%, indicating a benefit favoring the combination of dipyridamole plus aspirin. The only outcome that was reduced by the combination was nonfatal stroke (183 events vs 236 events; for nonfatal MI, the results were 150 events vs 134 events, and for vascular death were 286 events vs 279 events). None of these differences were statistically significant.

There has been only one trial using extended-release dipyridamole: ESPS-2.[132] In this study,[132] 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 as follows: 25 mg of aspirin, 200 mg of extended-release dipyridamole, 25 mg aspirin plus 200 mg of 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 risk of stroke—nonfatal and fatal—by 23%. The absolute risk reduction was 3% at 2 years, or approximately 1.5% annually.

In summary, aspirin reduces the odds of the composite outcome of stroke, MI, or vascular death in all high-risk patients with symptomatic atherosclerosis by approximately 23%. It reduces the odds of stroke alone by approximately 25%. In trials limited to stroke/TIA patients, aspirin reduced the odds of the composite outcome of stroke, MI, or vascular death by only 16%. In stroke/TIA patients, ticlopidine is more effective than placebo, but has at least a 5% incidence of bothersome adverse effects, a 0.9% incidence of severe neutropenia, and a small risk of TTP. The serious side effects of ticlopidine have led many experts to largely abandon its use. In stroke patients clopidogrel produces a benefit similar to aspirin for prevention of stroke or the outcome cluster of stroke, MI, or vascular death. The safety profile of clopidogrel is comparable to aspirin and safer than ticlopidine. Compared to placebo, dipyridamole in combination with aspirin reduces the risk of the composite outcome of stroke, MI, or vascular death in patients with symptomatic atherosclerosis by approximately 30%.[117] In comparison with placebo, extended-release dipyridamole in combination with aspirin reduced the risk of stroke in patients with stroke/TIA by 37% in ESPS 2, which is nearly identical to the 38% stroke risk reduction that was obtained with the combination of standard dipyridamole and aspirin in a previous similar trial (ESPS 1).[143] When compared with aspirin, the combination of extended-release dipyridamole produced a 23% reduction in stroke. Although inadequately studied, the combination does not appear to provide benefit over aspirin alone for reducing MI.

No study has performed a direct comparison of clopidogrel with the combination of extended-release dipyridamole and aspirin. However, each of these two therapies has been directly compared with aspirin in cerebrovascular patients (Fig 6). The comparisons in Figure 6 of these antiplatelet trials and drugs are indirect and thus must be interpreted far more cautiously than direct comparisons. Based on this indirect comparison, the combination of extended-release dipyridamole and aspirin may be more effective that clopidogrel for prevention of stroke. The performance of antiplatelet drugs in separate trials varies because patient populations and protocols differ, and unrecognized biases may exist. No trial has performed a direct comparison between these alternative agents and physicians must make comparisons and clinical judgments based on the available data. Clearly, the relative benefit and safety of the various antiplatelet drugs, for various patients and vascular events, will remain uncertain unless very large trials directly comparing them are conducted.
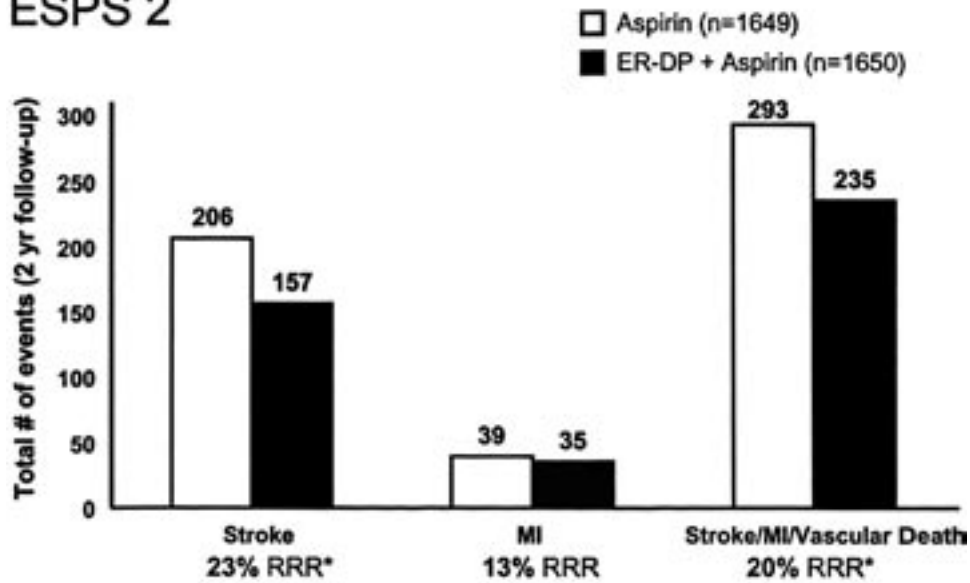
Ongoing trials will provide more information regarding the relative benefit of one antiplatelet strategy vs another in cerebrovascular patients. The PRoFESS trial (Prevention Regimen for Effectively avoiding Second Strokes) is directly comparing the combination of extended-release dipyridamole plus aspirin vs clopidogrel.

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

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 agent (**Grade 1A**). Aspirin at a dose of 50 to 325 mg qd; the combination of aspirin, 25 mg and

ESPS 2

Legend:
☐ Aspirin (n=1649)
■ ER-DP + Aspirin (n=1650)

Stroke
23% RRR*

MI
13% RRR

Stroke/MI/Vascular Death
20% RRR*

*Statistically significant
(For Stroke/MI/Vascular Death p=0.01; 95% CI 5.1 to 32.7)

CAPRIE Study

Legend:
☐ Aspirin (n=3198)
■ Clopidogrel (n=3233)

Stroke
8% RRR

MI
0% RRR

Stroke/MI/Vascular Death
7% RRR
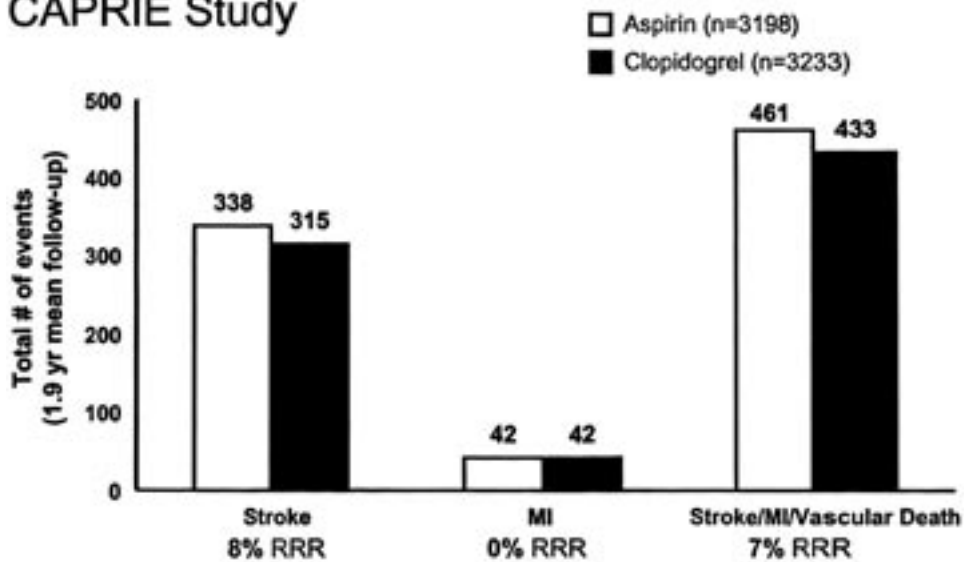
Results not statistically significant
(For Stroke/MI/Vascular Death p=0.26; 95% CI -5.1 to 18.7)

FIGURE 6. Outcome events in the ESPS 2 study (top) and from the stroke subgroup of the CAPRIE study (bottom). RRR = relative risk reduction; ER = extended-release; DP = dipyridamole.

extended-release dipyridamole, 200 mg bid; or clopidogrel, 75 qd, are all acceptable options for initial therapy.

4.1.2. In patients receiving aspirin who are at moderate to high risk of bleeding complications, we recommend using low doses of aspirin, 50 to 100 mg/d (**Grade 1C+**).

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

Underlying values and preferences: This recommendation to use the combination of aspirin and extended-release dipyridamole or clopidogrel over aspirin places a relatively high value on a small absolute risk reduction in stroke rates, and a relatively low value on minimizing drug expenditures.

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

4.2 Prevention of noncardioembolic cerebral ischemic events: oral anticoagulants

New data from large, well-designed, randomized trials assess 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[144] 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 ICHs) 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)[145] 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 WARSS failed to find a benefit of warfarin over aspirin for patients with patient foramen ovale, 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 results of the Warfarin vs Aspirin for Symptomatic Intracranial Disease (WASID) study[146] were recently announced. This trial failed to show a benefit of warfarin (target INR 2 to 3) vs. aspirin (1300 mg/day) for preventing stroke and vascular death in patients with symptomatic stenosis of a major intracranial artery. An ongoing trial, the European-Australian Stroke Prevention in Reversible Ischemia Trial (ESPRIT) is comparing anticoagulation with an INR of 2 to 3 versus either aspirin (30 to 325 mg) or aspirin plus entended-release dipyridamole 200 mg bid for secondary stroke prevention.[147]

Despite the lack of data from well-designed randomized trials, some neurologists prescribe oral anticoagulant therapy for selected patients who have had recent noncardioembolic strokes or TIAs.[148] Based on favorable results in case series and nonrandomized studies, some experts recommend oral anticoagulants for specific patient populations, including patients with cervical artery dissection, severe carotid stenosis prior to endarterectomy, antiphospholipid antibody syndrome, and coagulation factor deficiencies. Whether anticoagulants are superior to antiplatelet agents for these indications is unknown.

Recommendations

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

4.2.2. For patients with noncardioembolic stroke with well-documented prothrombotic disorders, we suggest oral anticoagulation over antiplatelet agents (**Grade 2C**).

4.3. Prevention of cerebral ischemic events in patients undergoing carotid endarterectomy: antiplatelet agents

One randomized trial—the ASA and Carotid Endarterectomy trial—has addressed this issue. See section 4.1 for the evidence summary.

Recommendation

4.3. In patients undergoing carotid endarterectomy, we recommend aspirin, 81 to 325 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 approximately 50% of all cardiogenic emboli. In addition, several other cardiac lesions can cause cardioembolic stroke. Other high-risk sources of cardiogenic embolism include mitral stenosis, mechanical prosthetic valves, recent MI, 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.[90,149] 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 strands.

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.[150] 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.[149] Rapid recovery from major hemispheric deficits or presentation with depressed level of consciousness is suggestive of cardioembolic stroke.[150] 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.[151] 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 risk of stroke and recurrent embolic events vary with different cardiac disorders, it is clinically useful to divide potential cardiac sources into high-risk and low-risk categories (Table 3).

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 chapter on Antithrombotic Therapy in Atrial Fibrillation). Patients who have already suffered a stroke are at high risk of subsequent cardioembolic emboli.

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. Only two large randomized studies have specifically evaluated the efficacy of antiplatelet agents for secondary prevention of cardiac embolism. The European Atrial Fibrillation Trial[152] 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,[152] aspirin was associated with a 16% reduction in the relative risk of stroke; however, this difference was not statistically significant. The Studio Italiano Fibrillazione Atriale study[153] 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, MI, 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 efficacy 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 (see chapter on Antithrombotic Therapy in Atrial Fibrillation in this Supplement) of aspirin in patients with atrial fibrillation who have not yet had a stroke suggest a relative risk reduction of approximately 21% and provide further indirect evidence in support of antiplatelet agents in patients with cardioembolic stroke.

Recommendation

4.4.2. For patients with cardioembolic stroke who have contraindications to anticoagulant therapy, we recommend aspirin (**Grade 1A**).

4.4.3 Patients following MI

The long-term risk of stroke following the acute phase of MI is 1 to 2%/yr. Cardioembolic mechanisms include the formation of mural thrombi over akinetic or hypokinetic segments, within ventricular aneurysms, and due to ischemic cardiomyopathies with left ventricular dysfunction. The size of the MI, severity of left ventricular dysfunction, and age are independent factors affecting stroke risk.[154,155] Patients with ejection fractions of < 28% may be at significantly higher risk for stroke.[155]

The Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis-2 trial[156] enrolled patients who had experienced a first MI or unstable angina within the preceding 8 weeks and, after a median follow-up of 1 year, found oral anticoagulation was superior to aspirin therapy in reducing recurrent MI, stroke, or death, with no increase of hemorrhagic stroke. There were five strokes in the 336 patients receiving aspirin, and 0 in the 325 patients receiving warfarin.[156]

Long-term anticoagulation with warfarin for survivors of MI has been demonstrated in several studies[157–159] to reduce the absolute risk of stroke by approximately 1%/yr at the expense of an increased rate of hemorrhagic stroke. The net benefit of chronic anticoagulation appears to be very small for unselected survivors of MI.[160]

The risk of stroke in patients with chronic left ventricular aneurysms is low, and long-term anticoagulation is generally not recommended unless the thrombus is mobile or pedunculated.[161] Results from additional randomized studies are needed to better identify patient subgroups most likely to benefit from long-term anticoagulation after MI. See the chapter for recommendations regarding patients with MI, elsewhere in this Supplement.

Table 3—Cardioembolic Sources

Major Risk	Minor or Uncertain Risk
Atrial fibrillation	Mitral valve prolapse
Mitral stenosis	Mitral annular calcification
Prosthetic mechanical valves	PFO
Recent MI	Atrial septal aneurysm
Left ventricular thrombus	Calcific aortic stenosis
Atrial myxoma	
Infective endocarditis	
Dilated cardiomyopathies	
Marantic endocarditis	

4.4.4 Patients with aortic atheromata

Mounting evidence implicates complex atherosclerotic aortic plaques as a significant independent risk factor for embolic stroke.[91,162,163] Transesophageal 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.[91,95,164,165] In one study, the annual risk of stroke was 33% in patients with protruding plaques of ≥ 5 mm in the thoracic aorta, compared with 7% in matched control subjects.[162] A French study[95] followed up 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 ≥ 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.[165,166]

No randomized trials have evaluated the role of any antithrombotic therapies in patients with aortic atheroma. Two studies[167,168] 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[169] of 519 patients with aortic plaques > 4 mm found that statins (OR, 0.39; 95% CI, 0.24 to 0.62; p = 0.0001), but not oral anticoagulation (OR, 1.18; 95% CI, 0.91 to 1.54; p = 0.21) or antiplatelet therapy (OR, 0.77; 95% CI, 0.51 to 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.[170,171]

Recommendation

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

4.4.5 Patients with PFO

A PFO is detected by contrast echocardiography in approximately 20% of normal individuals.[172] In young stroke patients, PFOs are detected in approximately 40%; in young patients with otherwise cryptogenic stroke, the rate of PFO detection may be ≥ 50%.[92,172–177] 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 to 10).[92,172–177] This overrepresentation of PFOs in young patients, particularly in those with no other explanation for

their stroke, implies that the PFO could be the etiology of many cryptogenic strokes, particularly in young patients.

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.[175] Among stroke patients with PFOs, the risk of stroke recurrence is estimated to be only 1 to 2%/yr.[172,178] Patients with complex PFOs (*eg,* the combination of a large PFO and atrial septal aneurysm) may be at substantially higher risk for recurrent events.[174] One follow-up study on patients < 55 years old with cryptogenic stroke, who all had transesophageal echocardiographic 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 receiving aspirin, 300 mg/d.[179] In the PICSS trial,[179a] 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 receiving warfarin (compared to patients receiving aspirin), but this result was not significant.

PFO closure is an appealing 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 to 4%/yr.[178,180–182] Percutaneous closure is technically feasible and has the potential to avoid major surgical morbidity. Stroke recurrence rates in published reports are < 4%/yr.[183–189] A number of devices are presently in clinical use, although to date none has been granted US 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

4.4.5. In patients with cryptogenic ischemic stroke and a PFO, we recommend antiplatelet therapy over no

therapy (**Grade 1C+**), and suggest antiplatelet therapy over warfarin (**Grade 2A**).

Remark: For patients with evidence of DVT, we recommend anticoagulation.

4.4.6 Mitral valve strands and prolapse

Mitral valve strands, also known as *Lambl's excrescences*, are filamentous mobile processes attached to the mitral valve. These strands are also occasionally seen on the aortic valve on transesophageal echocardiography.[190] Some studies[191,192] 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.

Mitral valve prolapse was implicated as a potential source of embolic stroke in the 1970s.[193] However, several case control studies[174,194] in young stroke patients did not confirm this association using currently accepted echocardiographic criteria. 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.[195,196]

Recommendation

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

4.4.7 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 chapter 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 chapters 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.[197] Diagnosis of the thrombosed sinus, although frequently suspected on CT scan, is based on increased signal on both T1- and T2-weighted MRI and magnetic resonance angiography. Conventional angiography is rarely needed when MRI is available.[198] 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 receiving oral contraceptives.[199] The prognosis of CVST is generally much better than previously thought, but remains largely unpredictable.

5.1 Anticoagulation for CVST

Two small, randomized trials[200,201] have shown somewhat differing results. One randomized study compared dose adjusted unfractionated heparin (prothrombin time at least two 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 2 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).[200] 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.[200]

The other randomized trial[199] 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. Patients with intracranial bleeding caused by the CVST were also included. Overall, after 12 weeks, 13% (3 of 30 patients) of those 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 relative risk reduction of 38% in the nadroparin group, a difference that did not reach statistical significance. There were two fewer deaths in the nadroparin group (two deaths vs four deaths) 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 meta-analysis, and the results from observational studies,[197,201] 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 intra-thrombus infusion of a thrombolytic agent together with IV heparin are under investigation.[198,202]

Recommendation

5.1. In patients with venous sinus thrombosis, we recommend that clinicians use unfractionated heparin (**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 use of vitamin K antagonists for 3 to 6 months (target INR, 2.5; range, 2.0 to 3.0) [**Grade 1C**]. For patients with venous sinus thrombosis associated with heparin-induced thrombocytopenia, see the chapter by Warkentin *et al.* in this Supplement for recommendations.

Summary of Recommendations

1.0 Acute Ischemic Stroke: Thrombolytic Therapy in Acute Stroke

1.1 IV tPA for AIS within 3 h of symptom onset

1.1.1. For eligible patients (see inclusion and exclusion criteria listed in body of text), we recommend administration of IV tPA in a dose of 0.9 mg/kg (maximum of 90 mg), with 10% of the total dose administered 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 assumes a relatively higher value on long-term functional improvement and a relatively lower value on minimizing the risk of ICH in the immediate peristroke period.

1.1.2. For patients with extensive (more than one third of the MCA territory) and clearly identifiable hypodensity on CT, we recommend **against** thrombolytic therapy (**Grade 1B**).

1.2 IV tPA for AIS between 3 h to 6 h of symptom onset

1.2. For unselected patients with AIS of > 3 h but < 6 h, we suggest clinicians **not** use IV tPA (**Grade 2A**).

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 ICH and death, and a relatively high degree of risk aversion.

1.3 IV streptokinase for AIS between 0 and 6 h of symptom onset

1.3. For patients with AIS, we recommend **against** streptokinase (**Grade 1A**).

1.4 Intra-arterial thrombolysis for AIS

1.4.1. For patients with angiographically demonstrated MCA occlusion and no signs of major early infarction on the baseline CT scan, who can be treated within 6 h of symptom onset, we suggest use of intra-arterial thrombolytic therapy with tPA (**Grade 2C**).

1.4.2. For patients with acute basilar artery thrombosis and without major CT/MRI evidence of infarction, we suggest intra-arterial thrombolysis with tPA (**Grade 2C**).

2.0 AIS: Patients Not Eligible for Thrombolysis

2.1 Anticoagulants for altering outcomes among acute stroke in patients not eligible for thrombolysis

2.1. For patients with AIS, we suggest clinicians **not** use full-dose anticoagulation with IV, subcutaneous, or low molecular weight heparins or heparinoids (**Grade 2B**).

2.2 Antiplatelet agents for altering outcomes in acute stroke in patients not eligible for thrombolysis

2.2. For patients with ischemic stroke who are not receiving thrombolysis, we recommend early aspirin therapy, 160 to 325 mg/d (**Grade 1A**).

2.3 Antithrombotic therapy for prevention of DVT and PE in AIS

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

2.3.2. For patients who have contraindications to anticoagulants, we recommend use of intermittent pneumatic compression devices or elastic stockings (**Grade 1C**).

3.0 DVT/PE Prophylaxis in Patients with Intracerebral Hematoma (ICH)

3.1 Heparin for DVT/PE prophylaxis in patients with ICH

3.1. In patients with an acute ICH, we recommend the initial use intermittent pneumatic compression (**Grade 1C+**). In stable patients, we suggest low-dose subcutaneous heparin may be initiated as soon as the second day after the onset of the hemorrhage (**Grade 2C**).

Underlying values and preferences: The recommendation for subcutaneous heparin assumes a relatively low degree of risk aversion.

4.0 Stroke Prevention

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 agent (**Grade 1A**). Aspirin at a dose of 50 to 325 mg qd; the combination of aspirin, 25 mg, and extended-release dipyridamole, 200 mg bid; or clopidogrel, 75 mg qd, are all acceptable options for initial therapy.

4.1.2. In patients receiving aspirin who are at moderate-to-high risk of bleeding complications, we recommend using low doses of aspirin, 50 to 100 mg/d (**Grade 1C+**).

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

Underlying values and preferences: This recommendation to use the combination of aspirin and extended-release dipyridamole or clopidogrel over aspirin places a relatively

high value on a small absolute risk reduction in stroke rates, and a relatively low value on minimizing drug expenditures.

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

4.2 Prevention of noncardioembolic cerebral ischemic events: oral anticoagulants

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

4.2.2. For patients with well-documented prothrombotic disorders, we suggest oral anticoagulation over antiplatelet agents (**Grade 2C**).

4.3 Prevention of cerebral ischemic events in patients undergoing carotid endarterectomy: antiplatelet agents

4.3. In patients undergoing carotid endarterectomy, we recommend aspirin, 81 to 325 mg/d, prior to and following the procedure (**Grade 1A**).

4.4 Prevention of cardioembolic cerebral ischemic events

4.4.1 Patients with stroke with underlying atrial fibrillation: anticoagulation

4.4.1. In patients with atrial fibrillation who have had 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

4.4.2. For patients with cardioembolic stroke who have contraindications to anticoagulant therapy, we recommend aspirin (**Grade 1A**).

4.4.4 Patients with aortic atheromata

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

4.4.5 Patients with patent foramen ovale (PFO)

4.4.5. In patients with cryptogenic ischemic stroke and a PFO, we recommend antiplatelet therapy over no therapy (**Grade 1C+**), and suggest antiplatelet agents over anticoagulation (**Grade 2A**).

4.4.6 Mitral valve strands and prolapse

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

5.0 Cerebral Venous Sinus Thrombosis

5.1 Anticoagulation for cerebral venous sinus thrombosis

5.1. In patients with venous sinus thrombosis, we recommend that clinicians use unfractionated heparin (**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 oral anticoagulation for 3 to 6 months (target INR, 2.5; range, 2.0 to 3.0) [**Grade 1C**].

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