Antithrombotic and Thrombolytic Therapy for Ischemic Stroke

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Abbreviations: ACE = ASA and Carotid Endarterectomy; 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; FDA = Food and Drug Administration; GOS = Glasgow Outcome Scale; ICH = intracerebral hematoma; INR = international normalized ratio; IST = International Stroke Trial; MAST = Multicentre Acute Stroke Trial; MCA = middle cerebral artery; MI = myocardial infarction; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; NINDS = National Institute of Neurological Disorders and Stroke; OR = odds ratio; PE = pulmonary embolism; PFO = patent foramen ovale; pro-UK = recombinant pro-urokinase; TASS = Ticiplidine Aspirin Stroke Study; TIA = transient ischemic attack; TOAST = Trial of ORG 10172 in Acute Stroke Treatment; tPA = tissue plasminogen activator; TTP = thrombotic thrombocytic purpura

ISCHEMIC STROKE

Ischemic stroke is a syndrome of multiple etiologies and protean clinical manifestations. The optimal use of antithrombotic therapies for stroke treatment or prevention is guided by the specific pathogenesis (Fig 1, 2) and clinical features. Patients who are at increased risk for ischemic stroke can be identified (Fig 3). Atherosclerosis of the arteries, large and small, that supply the brain is the most common cause of ischemic stroke. Atherosclerosis of the proximal aorta is also a source of atherogenic brain emboli. Large-artery atherosclerotic infarction occurs when there is an impediment to normal perfusion, usually caused by a severe arterial stenosis or occlusion due to atherosclerosis and coexisting thrombosis or artery-to-artery embolism. Microatheroma, lipohyalinosis, and other occlusive diseases of the small penetrating brain arteries are the most frequent causes of small, subcortical "lacunar" infarcts. About 20% of ischemic strokes are due to 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, about 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 arteries. Most of these occlusions resolve within a few days, suggesting transient embolic or thrombotic obstruction. Thus, the specific pathogenesis of stroke in individual patients is sometimes difficult to elucidate, and determining the optimal choice of antithrombotic therapy for prevention of stroke worsening or recurrence is challenging.

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1. ACUTE ISCHEMIC STROKE

1.1. Thrombolytic Therapy

Thrombolytic therapy for the treatment of acute ischemic stroke has been the subject of recent intense investigation. In the past several years, nine randomized, placebo-controlled trials have been reported using IV recombinant tissue plasminogen activator (tPA), streptokinase, or intra-arterial recombinant pro-urokinase (r-pro-UK).1–9 The 1995 landmark report from the National Institute of Neurological Disorders and Stroke (NINDS) recombinant tPA Stroke Study Group demonstrated substantial benefit from the careful use of IV tPA in patients with acute ischemic stroke of < 3-h duration.1 In 1996, based on the strength of the NINDS report, the US Food and Drug Administration (FDA) approved tPA for use in early acute ischemic stroke. This ushered in a new era in acute stroke management requiring that stroke be recognized and treated as a time-critical emergency. Additional studies have helped to better define the safety, efficacy, and optimal use of thrombolytic therapy in acute stroke.

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 reengineering of stroke-care systems. To date, and to our knowledge, only the United States and Canada have regulatory approval for tPA use in stroke.

Background: The rationale for thrombolytic therapy is based on the recognition that most ischemic strokes are caused by thrombotic or thromboembolic arterial occlusions.10,11 Pathologic and angiographic studies demonstrate the presence of occlusive clot in up to 80% of ischemic strokes.10,12 Neuronal death and brain infarction evolve in a time-dependent fashion determined by both the duration and severity of the ischemic insult.13,14 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. Considerable experimental evidence using thrombolytic agents in animal stroke models shows that antologous clots can be effectively lysed by thrombolytics without excessive risk of brain hemorrhage, and functional neurologic recovery has been demonstrated.14–17 Coexistent hypertension may be a major factor influencing the risk of brain hemorrhage associated with thrombolytic therapy.18,19 The concomitant use of other antithrombotic agents, such as the combination of streptokinase and aspirin, increases the risk of hemorrhagic transformation in experimental models.20,21

Early Studies: 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.22,23

Interest in thrombolytic therapy for acute ischemic stroke was rekindled due to 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.24–26 A meta-analysis of thrombolytic stroke studies reported by Wardlow and Warlow 27 in 1992 was encouraging and suggested that further clinical trials should be conducted in large numbers of patients.

Preliminary feasibility and safety trials in stroke patients ensued. von Kummer et al28 reported three cerebral hematomas and seven hemorrhagic transformations in 33 patients treated with tPA and heparin. Wolpert et al29 reported an 11% incidence of parenchymal hematoma in an open study of 104 patients given IV tPA within 8 hours of stroke onset. Hemorrhagic transformation was more common in patients who had hypertension, were treated beyond 6 hours after stroke onset, or received large doses of tPA. Studies also evaluated therapeutic efficacy based on the success of arterial recanalization. A Japanese randomized trial30 of 98 patients reported recanalization in 25.6% of the tPA-treated patients compared with a spontaneous recanalization rate of only 4.3% in placebo-treated patients. del Zoppo et al31 reported a 1-hour recanalization rate of 34.4% in an angiographic study of 93 patients treated with tPA. Recanalization rates varied with the site of occlusion, ranging from only 8% with extracranial occlusions of the internal carotid artery, to 26% and 38% with middle cerebral artery (MCA) stem and distal branch occlusions, respectively.

Pilot studies31,32 designed to define the safety and optimal dose of tPA for future large-scale trials were completed using 90-min and 180-min therapeutic windows. Based on these results, a dose of 0.9 mg/kg was selected for future large-scale trials.

Large-Scale Trials of tPA: IV tPA has been evaluated in four large-scale trials using different doses, therapeutic windows, and treatment protocols: the NINDS recombinant t-PA study,1,33,34 the European Cooperative Acute Stroke Study (ECASS)-I,3 the ECASS-II,3 and the ATLANTIS rt-PA (Alteplase) Acute Stroke Trial (parts A and B).7,7a

The NINDS rtPA Acute Stroke Study Group1 conducted a randomized, double-blind, placebo-controlled study and enrolled 624 patients to receive treatment within 3 hours of clearly defined symptom onset. A pretreatment CT scan was required to exclude the presence of intracerebral hemorrhage, along with 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 treatment. The tPA was given as a 10% bolus over 1 minute, and the remainder of the total dose was infused over 60 minutes. In order to reduce the risk of intracerebral hemorrhage associated with hypertension, strict treatment algorithms were developed to monitor and maintain BP of < 185 mm Hg systolic and 110 mm Hg diastolic. Patients who required aggressive measures to attain pretreatment BP below these limits were not enrolled.

In part 1 of the NINDS study,1 291 patients were enrolled to assess early neurologic recovery. Early treatment response was measured using the National Institutes of Health Stroke Scale (NIHSS) 24 hours after enrollment, and an improvement of four or more points or a complete resolution of the neurologic deficit was considered a positive response. In part 2 of the NINDS study,1 333 patients were enrolled and the primary outcome measure was the percentage of patients with minimal or no disability at 3 months, as measured using a global test statistic of four stroke scales (NIHSS, Barthel Index [BI], modified Rankin Scale [mRS], Glasgow Outcome Scale [GOS]) and by each scale individually.

Combined data from parts 1 and 2 were reported because the results of part 1 were unknown before part 2.

Figure 1. The most frequent sites of arterial and cardiac abnormalities causing ischemic stroke.

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.
was completed. 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 odds ratio (OR) for favorable outcome with tPA was 1.7 (confidence interval [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 3 months was 17% in the tPA-treated group and 21% in the placebo-treated group (p = 0.30). Symptomatic intracerebral hemorrhage 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

Two variables were associated with an increased risk of intracerebral hemorrhage in patients treated with tPA: the severity of neurologic deficit as measured on the NIHSS score (OR, 1.8; 95% CI, 1.2 to 2.9), and brain edema or mass effect on the pretreatment CT scan (OR, 7.8; 95% CI, 2.2 to 27.1).12 Despite the increased risk of hemorrhage, patients with severe strokes were more likely to have favorable outcomes if treated with tPA (adjusted OR, 4.3; 95% CI, 1.6 to 11.9). Patients with edema or with mass effect on CT were also more likely to have a favorable outcome with tPA (adjusted OR, 3.4; 95% CI, 0.6 to 20.7), although this difference was not statistically significant. The benefits realized at 3 months with tPA therapy were achieved without early excess in morbidity and mortality due to intracerebral bleeding.

The benefits of tPA demonstrated in the NINDS study are durable and sustained during long-term follow-up.25 At 12 months, the global statistic favored the tPA-treated group (OR for a favorable outcome, 1.7; 95% CI, 1.2 to 2.3) and the tPA-treated patients were at least 30% more likely to have minimal or no disability than the placebo-treated patients. The difference favoring tPA in absolute terms ranged from 11 to 13%, depending on the outcome variable, essentially the same at 1 year as at 3 months. There was no significant difference in mortality at 12 months (24% in the tPA group vs 28% in the placebo group).

The ECASS-I trial2 was a multicenter, double-blind, 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 mRS 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 populations (patients without protocol violations). In the target population analysis, there was a significant difference of one point in the mRS 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 (mRS, 0 or 1; p < 0.05). Other predefined secondary end points, including the combined BI and mRS, 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 intracerebral hemorrhages. However, the incidence of major parenchymal hemorrhages was 19.5% 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 (hypointenuation exceeding one third of the MCA territory or diffuse swelling of the entire hemisphere) on CT scan (OR, 3.5; 95% CI, 2.3 to 5.3) were associated with increased risk of hemorrhagic infarction. The ECASS investigators concluded that tPA might be effective when given within 6 h of stroke onset, provided there are no major signs of infarction on the pretreatment CT scan.2

Differences between the ECASS-I and NINDS trials 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.3 In NINDS, half of the patients (> 300) were enrolled < 90 min from symptom onset, and a post hoc analysis has shown that patients treated early had better outcomes than those treated later.

**FIGURE 3.** Annual risk of stroke or vascular death among patients in various high-risk subgroups. Adapted from Wilterdink and Easton.101
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 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 a double-blind fashion to treatment with 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 mRS at 90 days, dichotomized as a favorable (mRS, 0 or 1) or unfavorable (mRS, 2 to 6) outcome. In the intention-to-treat analysis, 40.3% of tPA-treated patients (n = 222) treated with tPA vs 46% of placebo-treated patients (n = 180) in the placebo group (absolute difference, 3.7%; p = 0.277). A post hoc analysis of mRS scores dichotomized for independence (favorable mRS, 0 to 2) or death and dependency (mRS, 3 to 6) showed favorable outcomes in 54.3% of patients (n = 222) treated with tPA vs 46% of patients (n = 180) in the placebo group (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 intracranial hemorrhage occurred in 8.8% of the tPA-treated patients vs 3.4% in placebo-treated patients.

The differences in efficacy between the 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 treatments, 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 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 FDA approval of tPA in the first 3 h, part B was modified to a 3- to 5-h window. The protocol was similar to the NINDS study except for the time windows. A total of 142 patients were randomized in part A, and an intent-to-treat population of 613 was randomized in part B. Analysis of the target population is 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 because 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 intracerebral hematoma (ICH) was 1.1% vs placebo with 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 the ATLANTIS trial, 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 the ATLANTIS trial had milder strokes on average and were treated quite late.

See Table 1 for a comparison of the key outcomes of NINDS, ECASS-I, ECASS-II, and ATLANTIS part B.

**Streptokinase Trials:** Three placebo-controlled trials of IV streptokinase for acute stroke, the Multicentre Acute Stroke Trial (MAST)-Italy, the MAST-Europe, and the Australian Streptokinase Trial, were initiated but subsequently stopped prematurely by safety committees due to unfavorable rates of early mortality and intracranial bleeding associated with streptokinase. MAST-Italy was stopped after 622 patients were randomized to treatment within 6 h of stroke-symptom onset. Treatment consisted of IV streptokinase, 1.5 million U given over 1 h; aspirin, 300 mg/d for 10 days, both drugs; or control treatment. 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-treated group. The rate of symptomatic intracranial hemorrhage was 6% in streptokinase-treated patients, 10% in those who received combined therapy, 2% in patients receiving only aspirin, and 0.6% in the control group. There was a nonsignificant reduction in death and disability at 6 months in patients treated with streptokinase.

Before the safety committee halted the trial, MAST-Europe randomized 270 patients with stroke of <6-h duration. Patients were treated with streptokinase (1.5 million U) or placebo. Symptomatic intracranial hemor-

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**Table 1—Data From the Four Major Trials of IV tPA for Stroke, Comparing Dose, Therapeutic Window, Mortality, and OR for Benefit of tPA in the Incidence of Death and Dependency**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, No.</th>
<th>Dose, mg (Maximum)</th>
<th>Window h</th>
<th>Symptomatic ICH</th>
<th>Mortality</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>NINDS</td>
<td>624</td>
<td>0.9 (90)</td>
<td>≤ 3</td>
<td>tPA, %</td>
<td>Placebo, %</td>
<td>tPA, %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.4</td>
<td>0.6</td>
<td>17.4</td>
</tr>
<tr>
<td>ECASS-I</td>
<td>620</td>
<td>1.1 (100)</td>
<td>≤ 6</td>
<td>19.8*</td>
<td>6.5*</td>
<td>22</td>
</tr>
<tr>
<td>ECASS-II</td>
<td>800</td>
<td>0.9 (90)</td>
<td>≤ 6</td>
<td>8.8</td>
<td>3.4</td>
<td>10.5</td>
</tr>
<tr>
<td>ATLANTIS-B</td>
<td>547</td>
<td>0.9 (90)</td>
<td>3–5</td>
<td>7.0</td>
<td>1.1</td>
<td>11.0</td>
</tr>
</tbody>
</table>

*Parenchymal hematoma (symptomatic ICH not reported in ECASS-I).
rhage 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.

The Australian Streptokinase Trial randomized 340 patients within 4 h of stroke onset to receive either streptokinase (1.5 million U 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.

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

**Intra-arterial Thrombolysis Studies:** 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 angiography.

The PROACT trial treated 40 patients with MCA occlusions with either intra-arterial rpro-UK (n = 26) or placebo (n = 14). All patients received IV heparin. Treatment with the study drug was started a median of 5.5 h after symptom onset. Recanalization rates were significantly higher with rpro-UK (58%) than with placebo (14%; two-tailed p = 0.017). There was no significant difference in the rate of early symptomatic hemorrhagic transformation, which occurred in 15.4% of the rpro-UK-treated patients and 7.1% of the placebo-treated patients (2p = 0.64). Mortality rates and clinical outcomes at 90 days favored treatment with rpro-UK but did not reach statistical significance. Recanalization rates and the risk of brain hemorrhage were influenced by the dose of heparin.

PROACT II was designed to further test the efficacy and safety of intra-arterial rpro-UK in patients with MCA occlusion of < 6-h 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 angiographically confirmed MCA occlusions and were randomized to receive 9 mg of intra-arterial rpro-UK plus heparin (n = 121) or heparin alone (n = 59). The heparin dose was the same for both groups (2,000-U bolus and a 500-U/h infusion of heparin for 4 h). A clinically and statistically significant benefit favored rpro-UK in the primary outcome analysis, with 40% of treated patients recovering to a mRS of ≤ 2 compared with 25% of control patients (absolute risk reduction, 15%; p = 0.043; relative risk reduction, 60%). Mortality was 25% in the rpro-UK arm and 27% in the control group. Symptomatic intracranial hemorrhage occurred in 10% of rpro-UK-treated patients and 2% of control patients (p = 0.063). The recanalization rate (Thrombolysis In Myocardial Infarction [TIMI] grade 2 or 3 flow rates) was 66% for rpro-UK vs 18% for control (p < 0.001).

Patients recruited to PROACT II had moderate to severe strokes, with a median baseline NIHSS of 17. The median time to start of intra-arterial treatment was 5.3 h. Mechanical clot disruption was not permitted.

At present, use of intra-arterial thrombolytic therapy for ischemic stroke has not received FDA approval and should be limited to clinical trials or highly selected patients who provide informed consent. Intra-arterial thrombolysis should be administered only by physicians with expertise in stroke and neurointervention techniques. An integrated multidisciplinary effort is required to permit the early recognition and timely treatment of patients. Additional clinical trials are needed to identify optimal patient characteristics for intra-arterial therapy and to better define the safety, efficacy, and the most effective agents, doses, and delivery techniques.

**Meta-analysis of Thrombolytic Therapy:** Thrombolytic stroke trials are extraordinarily difficult to conduct and, to date, only modest numbers of patients have been evaluated. Meta-analysis, when appropriately applied to trials using similar agents and therapeutic windows, is useful to define risks and benefits of specific therapies.

Meta-analysis of trial results for patients treated with tPA within 3 h of symptom onset (n = 866) showed a very significant reduction in the rate of death or dependency, from 71.6% in control-treated patients to 57.7% with tPA (OR, 0.55; 95% CI, 0.41 to 0.72). This benefit translates to one additional independent survivor for every seven patients treated. Similar results were obtained in the Cochrane Systematic Review of treatment with tPA within 3 h. IV tPA given within 6 h of symptom onset (n = 2,764) also showed significant, though less robust, 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 intracranial hemorrhage from 3% in control subjects to 10% in treated patients (OR, 3.2; 95% CI, 2.4 to 4.3).

The Cochrane Stroke Review Group conducted a meta-analysis of 17 trials involving a total of 5,216 patients conducted since 1981, evaluating a variety of thrombolytic agents, regimes, and therapeutic windows. Overall, thrombolytic therapy was associated with an excess of early deaths (OR, 1.85; 95% CI, 1.48 to 2.32) and early symptomatic hemorrhages (OR, 3.53; 95% CI, 2.79 to 4.45). Despite the risks of hemorrhage, there was a reduction in death or dependency when thrombolytic therapy was administered within 6 h (OR, 0.83; 95% CI, 0.73 to 0.94). Considerable heterogeneity existed between trial protocols, with one study entering patients only in the first 90 min or 180 min after stroke onset, while others entered patients as late as 5 days or 2 weeks after onset.
Use of IV tPA in Clinical Practice: Published reports of clinical experience with tPA administered according to protocols similar to the NINDS trial have, in general, demonstrated safety profiles and rates of favorable outcome that mirror the NINDS results. In the Standard Treatment with Activase to Reverse Stroke study, the largest series reported, the rate of symptomatic intracerebral hemorrhage was 3% in 389 patients treated in academic and community medical centers. Others have reported symptomatic intracranial hemorrhage rates of 5.8% of 189 tPA-treated patients and rates of 7% and 6.6% in smaller studies. These complication rates compare favorably to the 6.4% symptomatic intracranial hemorrhage rate in the NINDS trial. Strict adherence to treatment protocols is strongly recommended to achieve a favorable risk-benefit profile. Recently, three patients have been described who received tPA for stroke treatment within a few days of symptoms suggestive of cardiac ischemia. These patients developed hemopericardium and life-threatening cardiac tamponade. Therefore, a careful history, searching for symptoms of recent myocardial ischemia or pericardial disease, may be appropriate prior to administering tPA for stroke treatment.

Evaluation of Baseline CT Scan

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. Patients with early radiographic evidence of major cerebral infarction defined as the presence of mass effect or ischemic hypodensity involving greater than one third of the MCA territory are at substantially greater risk for developing symptomatic intracranial hemorrhage following thrombolytic therapy and have been excluded from several large randomized trials (ECASS-I, ECASS-II, PROACT-II, ATLANTIS). In general, these patients should not receive tPA therapy.

Subtle or limited signs of early infarction on the CT scan are common and do not preclude the safe use of tPA for stroke treatment. 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.

The use of MRI rather than CT for selection of patients for thrombolytic therapy is under investigation. Preliminary data suggest that specific MRI profiles may identify patients who are particularly likely to benefit from thrombolytic therapy. In addition, MRI appears to be highly sensitive for identification of acute brain hemorrhage.

Defibrinogenating Agents in Acute Stroke

Ancrod is a thrombin-like defibrinogenating agent derived from a purified snake venom fraction, with a unique pharmacologic profile that may benefit patients with acute ischemic stroke. The depletion of fibrinogen produces effective anticoagulation and inhibits platelet aggregation. The reduction in fibrinogen also serves to reduce blood viscosity, thereby potentially increasing cerebral blood flow. Additionally, the products of defibrinogenation indirectly stimulate endogenous plasminogen activators, which may enhance clot lysis. Small ischemic stroke studies have demonstrated outcome trends favoring ancrod.

The STAT study randomized 500 patients to ancrod or placebo treatment initiated within 3 h of symptom onset. Treatment was given as a continuous 72-h infusion, followed by 1-h infusions at 96 h and 120 h. Ancrod dose adjustments were made to target plasma fibrinogen levels from 40 to 69 mg/dL. The primary efficacy end point was a BI of ≥ 95. The covariate-adjusted proportions of functional success were 42.2% in the ancrod-treated group vs 34.4% in placebo-treated patients (p = 0.041). Mortality rates were similar in the two groups. Symptomatic intracranial bleeding occurred in 5.2% of ancrod-treated patients and 2% of placebo-treated patients (p = 0.063). Ancrod has not been approved by the FDA and remains investigatory therapy. The European Stroke Treatment with Ancrod Trial is in progress and is designed to evaluate ancrod vs placebo treatment in 1,680 patients randomized to treatment within 6 h of symptom onset.

1.2. Patients Not Eligible for Thrombolysis

For acute cerebral infarction patients who are not eligible for IV recombinant tPA therapy, a variety of antithrombotic agents can be considered. Several anticoagulants (heparin, low-molecular-weight heparins, and heparinoids) and aspirin have been evaluated in clinical trials. The rationale for the use of antithrombotic therapy for treatment of acute ischemic stroke is based on two premises: (1) reduction of the risk of stroke progression or recurrent cerebral thromboembolism; and (2) prevention of venous thromboembolic complications such as deep venous thrombosis (DVT) and pulmonary embolism (PE).

The use of antithrombotic agents in an attempt to reduce the risk of stroke progression or recurrent embolism 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, 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.

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. In the North American Symptomatic Carotid Endarterectomy Trial, medically treated patients with transient ischemic attack (TIA) or stroke and ipsilateral carotid stenosis > 70% had a 26% risk of ipsilateral stroke at 2 years. Data from the Northern Manhattan Stroke Study indicated that the 30-day risk of recurrence was 8% for patients with extracranial atherosclerosis and 7.1% for those with intracranial atheroscle-
These risks were nearly sixfold greater than those for nonatherosclerotic stroke. Moreover, recurrent stroke risks from natural history studies are generally greater than those observed in the control groups of recent randomized trials that reported risks of 0.6 to 2.2%/wk.

Causes of worsening and recurrence in patients with large artery atherosclerotic stroke include propagation or progression of the thrombus, 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 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.

More recent nonrandomized studies 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 suggested a recurrence risk that approached 1%/d in the first 14 days; however, more recent studies have found the risk of early recurrence to be considerably lower.

The cause of an early recurrence in patients with cardioembolic stroke is usually another thrombus becoming dislodged from the intracardiac source, and the risk of early stroke recurrence is likely related to the underlying cardiac lesion. For example, one study found a high rate of early recurrence in a large group of cardioembolic stroke patients who had rheumatic heart disease, prosthetic valves, or documented intracardiac thrombi, but a significantly lower recurrence rate in atrial fibrillation patients.

Anticoagulants substantially reduce the 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 randomized clinical trial. The 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) in the patients who did not receive anticoagulants. More recent clinical trials have cast doubts on the efficacy of early anticoagulation for strokes with a cardioembolic source. For example, the recently published Heparin in Acute Embolic Stroke study randomized 449 patients with acute ischemic stroke (within 30 h after onset) to treatment with aspirin (160 mg/d) vs a high dose of the low-molecular-weight heparin, dalteparin (100 IU/kg subcutaneously bid). No difference in the frequency of early recurrent ischemic stroke or cerebral hemorrhage was detected. The timing of administration of IV anticoagulation can affect the risk-to-benefit ratio. Minimizing the risk of hemorrhagic transformation of an infarct while maximizing the reduction in early recurrence are the aims of early anticoagulation. A large infarct size, judged by neuroimaging findings or the clinical syndrome, and elevated BP’s are predictors of a greater risk of hemorrhagic transformation and warrant a delay in the use of anticoagulation.

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

Some strokes are difficult to reliably classify into these categories and have been labeled cryptogenic infarcts. These patients typically have no carotid bruit or TIA ipsilateral to the hemisphere affected by the stroke and no obvious history suggestive of cardiac embolism, and usually do not present with a lacunar syndrome. The CT or MRI scan performed may have normal findings, 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. Some experts treat these patients as though they have an acute cardiac embolism until the diagnostic cardiac testing is completed. 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. Optimal antithrombotic therapy for these etiologies has not been evaluated in randomized trials. Decisions about acute therapy for cryptogenic infarcts depend on a presumed mechanism for the stroke.

**Recent Studies of Anticoagulants for Acute Stroke Therapy:** Randomized trials using heparin, heparinoids, and aspirin have helped clarify the benefits and risks of antithrombotic agents for treatment of acute ischemic stroke.

Since 1980, to our knowledge, only a single randomized trial has evaluated IV heparin compared with placebo treatment for patients with acute stable stroke. No significant difference in stroke progression or neurologic outcome was detected in this relatively small study (n = 225).
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 treatment.

Subcutaneous administration of heparin was evaluated in the International Stroke Trial (IST). In this unblinded megatrial, 19,435 patients with suspected acute ischemic stroke from 467 hospitals in 36 countries were randomized within 48 h of onset (median, 19 h) to treatment with aspirin, subcutaneous heparin, both, or neither in a factorial design. Half were allocated 300 mg of aspirin and half to “avoid aspirin”; half were allocated unfractionated heparin administered subcutaneously in two different doses of 5,000 U bid or 12,500 U bid, and the remaining half to “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 hospital discharge or for 14 days, whichever was sooner, and at 6 months by telephone or postal questionnaire by each national coordinating center. The primary outcomes were death within 14 days, and death or dependency at 6 months. Secondary outcomes included recurrent ischemic stroke, hemorrhagic stroke, PE, or transfused or fatal extracranial hemorrhage within 14 days.

IST data were analyzed with the two heparin groups combined. There was no significant difference in 14-day mortality (heparin, 9.0% vs no heparin, 9.3%) or 6-month outcome (heparin, 62.9% dead or dependent vs no heparin, 62.9%). At 14 days, recurrent ischemic strokes were significantly reduced in the heparin groups (from 3.8 to 2.9%) but hemorrhagic stroke was significantly increased (from 0.4 to 1.2%), yielding no net benefit. In the subgroup of patients who presented with atrial fibrillation and acute ischemic stroke, heparin significantly reduced the risk of 14-day ischemic stroke recurrence from 4.9 to 2.8%, but an increased risk of hemorrhagic stroke (2.1% vs 0.4%) neutralized the potential benefits. Transfused or fatal extracranial hemorrhages were significantly more frequent among those allocated to heparin therapy. 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 IST 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 acute ischemic stroke with mixed results. In the Hong Kong trial, nadroparin-treated patients had better 6-month outcomes. In this trial, 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 completed in Europe, Canada, and Australia (the Fraxiparine in Ischemic Stroke Study) was unable to corroborate these beneficial effects. In this trial, 767 acute ischemic stroke patients were enrolled within 24 h into two dose groups and a placebo group. 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-treated group.

The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) evaluated the low-molecular-weight heparinoid danaparoid (ORG 10172) among 1,281 patients with ischemic stroke treated within 24 h of onset. In this multicenter, blinded, placebo-controlled trial, patients were treated for 7 days with an IV infusion of the heparinoid, and daily dose adjustments were based on antifactor Xa units. 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 favor-
able outcomes was significantly higher in the danaparoid group (33.9% vs 27.8%; p = 0.01). There was no significant reduction in stroke progression, 7-day mortality, or the risk of stroke recurrence or systemic embolic events. Subgroup analysis revealed a benefit in favorable outcome at 3 months for patients with large artery atherosclerotic stroke (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.

There is still uncertainty regarding the appropriate use of heparin and low-molecular-weight heparins for treatment of acute stroke, although more recent reviews have strongly discouraged the indiscriminate use of IV heparin. Minimizing the risk of hemorrhagic transformation of an infarct while maximizing the reduction in the early recurrence risk are the aims of the therapy. 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. Many 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 disappointing, improved study design may produce more definitive results in future studies restricted to hyperacute stroke patients.

Use of Antiplatelet Agents in Acute Stroke: Aspirin is the only antiplatelet agent that has been evaluated for the treatment of acute ischemic stroke. Data are now available from two recent large trials, the IST and the Chinese Acute Stroke Trial (CAST). These studies both found that the use of early aspirin in patients treated within 48 h of stroke onset (median time to randomization was 19 h in IST, and the mean time to randomization was 25 h in CAST) reduced both stroke recurrence risk and mortality.

Among 19,435 patients randomized in IST, aspirin-allocated patients had slightly fewer deaths within 14 days (9.0% vs 9.4%), significantly fewer recurrent ischemic strokes (2.8% vs 3.9%), no excess of hemorrhagic strokes (0.9% vs 0.8%), and a trend toward a reduction in death or dependence at 6 months (61.2% vs 63.5%).

In CAST, 21,106 patients with acute ischemic stroke within 48 h of onset were randomized to receive 160 mg/d of aspirin or a placebo for up to 4 weeks. The primary end points were death from any cause at 4 weeks and death or dependence at hospital 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 hospital discharge, there was a smaller proportion of patients who were dead or dependent in the aspirin-treated group (30.5% vs 31.6%; p = 0.08). In combination, the IST and CAST trials demonstrate that the use of aspirin in the treatment of acute ischemic stroke is safe and produces a small but definite net benefit. For every 1,000 acute strokes treated with aspirin, about 9 deaths or nonfatal stroke recurrences will be prevented in the first few weeks and approximately 13 fewer patients will be dead or dependent at 6 months.

**Antithrombotic Therapy for Prevention of DVT and PE:** DVT and PE are frequent complications of stroke, with about 5% of early deaths attributed to PE. Large trials performed in other high-risk groups (such as patients who underwent major surgery) indicate that heparin can reduce the risk of DVT and PE by about 60%. For acute stroke patients, few randomized trials have individually been able to demonstrate a significant decrement in the risk of these complications. An overview analysis in 1993 reviewed the results of 10 trials that evaluated heparin in 1,047 patients with acute ischemic stroke; an 80% reduction in DVT and a 58% reduction in PE were found. In the IST, there was a significant reduction in the frequency of fatal or nonfatal PE, from 0.8 to 0.5%, among those treated with 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 the TOAST study, DVTs were significantly reduced in the heparinoid-treated group compared with the placebo-treated group. DVT and PE prophylaxis is an essential reason to consider early anticoagulant therapy in acute stroke patients. For patients with contraindications to anticoagulants, intermittent pneumatic compression devices or elastic stockings are recommended (see chapter on prevention of venous thromboembolism).

**DVT/PE Prophylaxis in Patients With ICH:** Only one small study is available to address the risk of early prophylactic therapy with anticoagulants in patients with intracerebral hemorrhages. In this study, 22 patients with spontaneous intracerebral hemorrhage 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 therapy (5,000 U heparin sodium tid subcutaneously) 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.

2. Stroke Prevention

2.1 Antiplatelet Agents

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

The Antiplatelet Trialists conducted a major meta-analysis that assessed the effect of antiplatelet agents in patients with various manifestations of atherosclerosis. These studies included patients with unstable angina, MI, TIA, and stroke, as well as other patients at increased risk for atherothrombotic events. They aggregated the 73,247 high-risk patients who had been in trials lasting > 30 days, i.e., receiving long-term antiplatelet therapy. The Antiplatelet 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 Antiplatelet 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 about 27%. The odds reduction attributable to aspirin alone was 25%. They found that antiplatelet agents reduce the odds of a nonfatal stroke by 31%, nonfatal MI by about 35%, and vascular mortality by 18%.

The Antiplatelet Trialists also analyzed the differences in the response of patients > 65 and < 65 years old, 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 Antiplatelet 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 Antiplatelet Trialists found that whereas "all antiplatelet agents" reduced the odds of stroke, MI, or vascular death in "all high-risk patients" by 27%, the odds reduction in patients with prior stroke/TIA was only 22%. Additionally, Algra and van Gijn performed a mini-meta-analysis 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.

Aspirin: The Swedish Aspirin Low-Dose Trial compared aspirin, 75 mg/d, with placebo treatment 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 found for all doses of aspirin in similar patients.

The Dutch TIA Trial compared two dosage regimens of aspirin, 30 mg/d vs 273 mg/d, in 3,131 patients with minor stroke/TIA. The primary outcome measure was stroke, MI, or vascular death. The investigators found that aspirin, 30 mg/d, was no less effective than 273 mg/d, and there were fewer bleeding events with the lower dose.

These latter two trials, along with the earlier United Kingdom Transient Ischaemic Attack trial and the Algra and van Gijn mini-meta-analysis, led many clinicians to believe there are no important differences in daily doses of aspirin between 30 mg and 1,300 mg for preventing stroke and other vascular events. Also, low-dose aspirin is less gastrotoxic. Then in 1996, the European Stroke Prevention Study (ESPS)-II (see below) reported that aspirin, 50 mg/d, administered to patients following stroke or TIA reduced the risk of stroke, and stroke or death, by 18% and 13%, respectively. Consequently, the majority of clinicians worldwide currently recommend a daily dose of 325 mg or less for prevention of stroke. The acceptable dose range of aspirin for stroke prevention includes daily doses from as low as 30 mg to as high as 1,300 mg. In 1998, the FDA published their new recommendation that aspirin, 50 to 325 mg/d, be used for prevention of ischemic stroke.

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). ACE compared, head-to-head, aspirin at low doses (81 mg/d or 325 mg/d) vs high doses (650 mg/d or 1,300 mg/d) in 2,804 patients treated for a total of 3 months. There were no significant differences between low and high doses for any end point at 30 days, or for the end points of 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 3 months (p = 0.03). The ACE results
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.91 Two large trials92,93 assessed ticlopidine for the prevention of stroke and other vascular events in patients presenting with cerebrovascular symptoms.

The Ticlopidine Aspirin Stroke Study (TASS)92 enrolled 3,069 patients who presented within 3 months of suffering a minor stroke or TIA. Half were treated with aspirin, 650 mg bid, and half were treated with ticlopidine, 250 mg bid. The ticlopidine group had a 21% greater relative risk reduction for stroke compared with aspirin, and a 9% greater reduction in the end point cluster of stroke, MI, or vascular death at 3 years (intention-to-treat analysis).94

Serious GI adverse effects (e.g., 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 receiving 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 (i.e., six blood counts in 3 months).

The Canadian American Ticlopidine Study93 involved 1,072 patients who were enrolled after the occurrence of a major ischemic stroke. The patients were randomly allocated to treatment with ticlopidine, 250 mg bid, or matching placebo. Patients in this study who received placebo had an event rate for stroke, MI, or vascular death of 15.3%/yr, 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.

Taken together, these trials show that ticlopidine substantially reduces the risk of stroke and other vascular outcomes in patients with cerebrovascular disease, and TASS showed ticlopidine to be more effective than aspirin.

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 Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study.99 CAPRIE was a randomized, blinded, multicenter trial designed to assess the relative efficacy of clopidogrel (75 mg/d) and aspirin (325 mg/d) in reducing the risk of the composite outcome of ischemic stroke, 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, which provides a true net-benefit assessment, the relative risk reduction with clopidogrel was 9.5% (95% CI, 1.2 to 18.5). Finally, when the results in CAPRIE are analyzed using the Antiplatelet Trialists’ technique (i.e., 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 CAPRIE99 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 end point of stroke was 8% (95% CI, −7 to 21; p = 0.28).

Although there were no major differences between aspirin and clopidogrel in terms of safety, and adverse experiences were minimal, serious hemorrhages occurred at a slightly higher rate among patients taking aspirin (1.55% vs 1.38%). There were 10 patients in the clopidogrel group (0.10%) with significant reductions in neu-
trophils to <1,200 cells/μL, compared with 16 patients in the aspirin group (0.17%). Five patients in the clopidogrel group and four patients in the aspirin group had severe neutropenia (<450 cells/μL). The overall safety profile of clopidogrel is similar to that of 325 mg/d of aspirin. A recent report identified 11 cases of thrombotic thrombocytopenic purpura (TTP) associated with clopidogrel among >3 million patients who have received this agent. Ten of these 11 cases occurred within 2 weeks of initiation of clopidogrel therapy, and most responded favorably to plasma exchange, although two patients required ≥20 exchanges before clinical improvement.

The CAPRlE 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. The beneficial effects of clopidogrel for the combined vascular end point seem to be comparable to the effects of ticlopidine, without the negative adverse effects profile. When compared with aspirin, the effect of clopidogrel on reducing stroke appeared to be less than the effect of ticlopidine. This result could be explained by the play of chance. Alternatively, ticlopidine and clopidogrel may prevent strokes differently, the dose of clopidogrel tested may have been suboptimal, or perhaps the benefit of these agents in TIA patients is greater than that in stroke patients.

**Dipyridamole:** The Antiplatelet Trialists analyzed trials involving dipyridamole alone vs placebo, dipyridamole combined with aspirin vs placebo, and dipyridamole combined with aspirin vs aspirin alone.

Ten trials compared dipyridamole alone vs placebo (200 events in 1,474 patients) and showed a 23% odds reduction for stroke, MI, or vascular death favoring dipyridamole. Thirty-four trials (1,741 events in 13,718 patients) compared dipyridamole combined with aspirin vs placebo and showed a 28% odds reduction in stroke, MI, or vascular death favoring the combination.

The Antiplatelet Trialists analyzed 14 trials that compared the combination of dipyridamole plus aspirin vs aspirin alone (628 events in 5,317 patients) for prevention of the composite outcome of stroke, MI, or vascular death. One trial involved patients entered because of prior MI, three involved patients entered because of prior stroke/TIA, four because of postcoronary artery bypass grafting, three because of intermittent claudication, two because of noncoronary grafting, and one because of diabetes. The odds reduction for all vascular events was ~3%, indicating a slight (statistically nonsignificant) benefit favoring aspirin alone. The only outcome that was reduced by dipyridamole combined with aspirin was nonfatal stroke. The odds reduction was 12% and not statistically significant. Although there is no signal favoring dipyridamole plus aspirin over aspirin for reducing MI, the number of MI events in trials evaluating this combination is inadequate to conclude no benefit with confidence.

In 1996, the results of the ESPS-2 were published. Patients who had experienced either an ischemic stroke or TIA were studied in a multicenter, randomized, blinded, factorial, placebo-controlled study with four treatment groups and a 2-year follow-up for all patients. The four twice-daily treatments were as follows: aspirin, 25 mg; extended-release dipyridamole, 200 mg; aspirin, 25 mg, plus extended-release dipyridamole, 200 mg; 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), and that the combination of extended-release dipyridamole plus aspirin was additive and produced highly significant benefits (37% risk reduction) for stroke prevention. Extended-release dipyridamole combined with aspirin reduced the risk of stroke (nonfatal and fatal) by 23% vs aspirin alone. The absolute risk reduction was 3% at 2 years, or about 1.5% annually. When the results of the ESPS-2 are added to those of the 14 previous trials of dipyridamole combined with aspirin vs aspirin alone in various atherosclerosis patients, there is a significant 23% reduction for dipyridamole plus aspirin compared with aspirin in the odds of nonfatal stroke and a nearly significant 10% reduction in the odds of all vascular events, although all of the 10% is attributable to nonfatal strokes.

ESPS-2 was a cerebrovascular trial, in which patients with stroke or TIA were enrolled. When the results of ESPS-2 are added to those of the three previous cerebrovascular trials, there is a significant 25% reduction in the odds of nonfatal stroke for the combination of aspirin and dipyridamole vs aspirin alone and a significant 18% reduction in the odds of all vascular events, although again all of the 18% is attributable to nonfatal stroke.

**Comparison of the Efficacy of Antiplatelet Agents:** 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 about 25%. It reduces the odds of stroke by about 30%. 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 reduces the same composite outcome by about a third, but there is 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. Clopidogrel produces a benefit similar to ticlopidine for the outcome cluster of stroke, MI, or vascular death, but may be less effective for prevention of stroke. 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 about 25%. 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 dipyridamole and aspirin in a previous similar trial (ESPS-1). Although inadequately studied, the combina-
tion does not appear to provide benefit over aspirin alone for reducing MI.

Each of the alternative antiplatelet agents (ticlopidine, clopidogrel, and dipyridamole/aspirin) has been directly compared with aspirin in only one large study of cerebrovascular patients (Fig 6). The comparisons in Figure 6 of these three antiplatelet trials and agents are indirect and thus must be interpreted more cautiously than direct comparisons. The performance of antiplatelet agents in separate trials varies because patient populations and protocols differ, and unrecognized biases may exist. To our knowledge, no trials have performed direct comparisons 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.

To our knowledge, no clinical trials have directly addressed the issue of subsequent therapy for patients who experience recurrent episodes of brain ischemia while taking aspirin therapy. Many experts select an alternative antiplatelet agent, while others begin anticoagulant treatment. Although some experts add ticlopidine or clopidogrel to aspirin, the benefits and safety of these combinations for long-term therapy in stroke patients are unknown.

**Antiplatelet Agents for Secondary Prevention of Cardioembolic Stroke:** In general, studies of antiplatelet agents for stroke prevention have focused on patients with TIA 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 compared the efficacy of aspirin (300 mg/d) to placebo treatment in patients with atrial fibrillation who had suffered a stroke or TIA within the last 3 months. In this trial, aspirin was associated with a 16% reduction in the relative risk of stroke; however, this difference was not statistically significant. The Studio Italiano Fibrillazione Atriale study compared the efficacy of indobufen (a reversible inhibitor of cyclo-oxygenase) with warfarin (international normalized ratio [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 great enough to exclude a substantial difference between the efficacy of the two agents. Therefore, at present, only very limited data are available regarding the efficacy of antiplatelet agents for secondary prevention of cardioembolism. In general, oral anticoagulant therapy is the treatment of choice for secondary prevention of cardioembolic stroke (see below). For patients who have contraindications to anticoagulant therapy, antiplatelet agents are recommended.

### Figure 6

**Indirect comparison of the efficacy of alternative antiplatelet agents with aspirin in patients with cerebrovascular disease.** Major outcome events in three large trials that compared an alternative antiplatelet agent with aspirin therapy alone. These data suggest that each of the three alternative agents is more effective than aspirin alone for prevention of major vascular events. Data from ESPS-2 for the combined vascular end point obtained from Boehringer Ingelheim Pharmaceuticals; Ridgefield, CT (data on file). Data derived from Diener, Hass et al., Easton, and the CAPRIE Steering Committee.

![Figure 6](image_url)

#### Table 2—Cardioembolic Sources

<table>
<thead>
<tr>
<th>Major Risk</th>
<th>Minor or Uncertain Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>Mitral valve prolapse</td>
</tr>
<tr>
<td>Mitral stenosis</td>
<td>Mitral annular calcification</td>
</tr>
<tr>
<td>Prosthetic mechanical valves</td>
<td>PFO</td>
</tr>
<tr>
<td>Recent MI</td>
<td>Atrial septal aneurysm</td>
</tr>
<tr>
<td>Left ventricular thrombus</td>
<td>Calcific aortic stenosis</td>
</tr>
<tr>
<td>Atrial myxoma</td>
<td>Mitral valve strands</td>
</tr>
<tr>
<td>Infective endocarditis</td>
<td></td>
</tr>
<tr>
<td>Dilated cardiomyopathies</td>
<td></td>
</tr>
<tr>
<td>Marantic endocarditis</td>
<td></td>
</tr>
</tbody>
</table>

2.2. Oral Anticoagulants

**Primary and Secondary Prevention of Cardioembolic Stroke:** 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). Atrial fibrillation is the most common cause of cardiac embolism and is responsible for about 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 (Table 2).

The cause of 30 to 40% of all ischemic strokes remains undetermined, and cardiac mechanisms are suspected to account for a substantial percentage of these cryptogenic strokes. Advances in cardiac imaging now permit the frequent detection of additional potential cardiac sources of emboli, such as PFO, atrial septal aneurysm, aortic arch atheroma, and mitral valvular 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. However, clinical features such as the mode of onset (sudden or progressive) or the vascular territory involved are not sufficiently specific or sensitive indicators to establish the stroke mechanism. Rapid recovery from major hemispheric deficits or presentation with depressed level of consciousness is suggestive of cardioembolic stroke. The occurrence of multiple infarctions in different vascular territories or the history of systemic emboli increases the likelihood of a cardiac mechanism. Many patients with a potential cardiac source may also have concomitant vascular disease. Early angiographic demonstration of an embolic occlusion may be helpful to support the diagnosis and to exclude atherosclerotic disease and other arterial causes. Transesophageal echocardiography is more sensitive for detecting cardioembolic sources than transthoracic studies, particularly echocardiography is more sensitive for detecting cardioembolic stroke. The occurrence of multiple infarctions in different vascular territories or the history of systemic emboli increases the likelihood of a cardiac mechanism. Many patients with a potential cardiac source may also have concomitant vascular disease. Early angiographic demonstration of an embolic occlusion may be helpful to support the diagnosis and to exclude atherosclerotic disease and other arterial causes. Transesophageal echocardiography is more sensitive for detecting cardioembolic sources than transthoracic studies, particularly when searching for left atrial sources, atrial septal defects, and aortic atheroma. Because the risk of stroke and recurrent embolic events vary with different cardiac disorders, it is clinically useful to divide potential cardiac sources into high- and low-risk categories (Table 1).

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. Patients with ejection fractions of < 28% may be at significantly higher risk for stroke. Long-term anticoagulation with warfarin for survivors of MI has been demonstrated in several studies to reduce the absolute risk of stroke by about 1% per year at the expense of an increased rate of hemorrhagic stroke. The benefit of long-term anticoagulation is minimal for unselected survivors of MI. 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. Results from additional randomized studies are needed to better identify patient subgroups most likely to benefit from long-term anticoagulation after MI.

There is mounting evidence to implicate complex atherosclerotic aortic plaques as a significant independent risk factor for embolic stroke. 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. 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. A French study 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 prospective studies. To our knowledge, no randomized trials have been conducted to evaluate the role of any antithrombotic therapies in patients with aortic atheroma. Two studies showed a benefit of an oral anticoagulant over aspirin in patients with mobile thrombi in the aortic arch, but the studies were retrospective and nonrandomized; furthermore, hemorrhagic complications possibly outweighed the benefits of the anticoagulants. Concerns also exist regarding the possibility of anticoagulation increasing the risk of cholesterol embolism in these patients. Therefore, currently available data are inadequate to generate a treatment recommendation for patients with ischemic stroke thought to be caused by embolization of aortic atheroma. Either antiplatelet therapy or oral anticoagulation are considered acceptable options.

A PFO is detected by contrast echocardiography in about 20% of normal individuals. In young stroke patients, PFOs are detected in about 40%, and in young patients with otherwise cryptogenic stroke, the rate of PFO detection may be ≥ 50%. 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 control subjects (OR, 3.9; 95% CI, 1.5 to 10). 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. Among stroke patients with PFOs, the risk of stroke recurrence is estimated to be only 1 to 2% per year. Patients with complex PFOs (eg, the combination of a large PFO and atrial septal aneurysm) may be at substantially higher risk for recurrent events. Optimal therapy for secondary prevention of stroke in patients with PFOs is uncertain, and options include antiplatelet therapy, anticoagulants, or closure by surgery or a transcatheter device.

Mitral valve straddles, also known as Lambl's excrescences, are filamentous mobile processes attached to the mitral valve. These straddles are also occasionally seen on the aortic valve on transesophageal echocardiography. Some studies have implicated these straddles 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 since the 1970s. However, several case control studies in young stroke patients did not confirm this association using currently accepted...
therapy for selected patients who have suffered recent extended-release dipyridamole, 200 mg bid.

to 3 vs either aspirin (30 to 325 mg) or aspirin plus Prevention in Reversible Ischemia Trial, with an INR of 2 of aspirin. The other is the European-Australian Stroke Study, with a target INR of 1.4 to 2.8 compared to 325 mg populations. One is the Warfarin Aspirin Recurrent Stroke target INR with antiplatelet strategies in similar patient embolic stroke. Two ongoing trials are comparing a lower to 4.5 is not safe for secondary prevention of noncardiovascular 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. Two ongoing trials are comparing a lower target INR with antiplatelet strategies in similar patient populations. One is the Warfarin Aspirin Recurrent Stroke Study, with a target INR of 1.4 to 2.5 compared to 325 mg of aspirin. The other is the European-Australian Stroke Prevention in Reversible Ischemia Trial, with an INR of 2 to 3 vs either aspirin (30 to 325 mg) or aspirin plus extended-release dipyridamole, 200 mg bid.

Despite the lack of data from well-designed, randomized trials, some neurologists prescribe oral anticoagulant therapy for selected patients who have suffered recent noncardioembolic strokes or TIAs.1,3 Based on favorable results in nonrandomized studies, some experts recommend oral anticoagulants for specific patient populations, including individuals who have experienced a stroke or TIA while receiving an antiplatelet agent and patients with crescendo TIAs, cervical artery dissection, severe carotid stenosis prior to endarterectomy, antiphospholipid antibody syndrome, symptomatic intracranial large-artery stenosis, and coagulation factor deficiencies. Whether anticoagulants are superior to antiplatelet agents for these indications is unknown, and data from well-designed randomized trials are needed.

3. 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. Diagnosis of the thrombosed sinus, although frequently suspected on CT scan, is based on increased signal on both T1-weighted and T2-weighted MRI and magnetic resonance angiography. Conventional angiography is rarely needed when MRI is available. More than 100 cases 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. The prognosis of CVST is generally much better than previously thought, but remains largely unpredictable. Two small, randomized trials are available, with differing results. One randomized study compared dose-adjusted unfractionated heparin (partial thromboplastin 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. Of 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-treated group (p < 0.01). 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. The other randomized trial compared nadroparin (90 anti-Xa U/kg bid) to placebo treatment 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-treated group. Patients with intracranial bleeding caused by the CVST were also included. Overall, after 12 weeks, 13% of patients (3 of 30) in the anticoagulation group and 21% of patients (6 of 29) 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, both unfractionated and low-molecular-weight-heparin are safe and probably effective in CVST. It is unlikely that a randomized trial with an adequate number of patients will be performed in the near future. We
recommend heparin as first-line treatment, even in patients with hemorrhagic venous infarcts, followed by oral anticoagulation for a period of 3 to 6 months. Some experts do not recommend heparin for patients with large hemorrhagic venous infarcts with associated hematomas. In patients who demonstrate progressive neurologic deterioration despite adequate anticoagulation, other options such as local intrathrombus infusion of a thrombolytic agent together with IV heparin are under investigation.\textsuperscript{155,156}

### Recommendations

#### 1. Acute Ischemic Stroke

##### 1.1. Thrombolytic Therapy

**Acute Ischemic Stroke Treatment Within 3 h of Symptom Onset**

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

1.1.2. We recommend strict adherence to eligibility criteria for the use of IV tPA based on the NINDS trial protocol (see below for inclusion and exclusion criteria). Therapy should be initiated as soon as possible to optimize benefits (grade 1C+).

**Remarks**

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

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

1.1.3. We recommend thrombolytic therapy almost always be withheld in patients with evidence of major early infarct signs (clear evidence of extensive early edema/mass effect) on the pretreatment CT scan (grade 1B).

**Remark:** Treatment should be supervised by physicians with expertise in stroke management and CT scan interpretation, and tPA treatment is not recommended if the time of symptom onset is uncertain or if symptoms have been present for $>3$ h. Some experts recommend that, if possible, efforts should be made to demonstrate a large artery intracranial occlusion using modern neuroimaging techniques prior to administration of tPA. Treatment should not be unduly delayed in order to facilitate vascular imaging. Adequate hospital facilities and personnel are required for administration of thrombolytic therapy as well as for monitoring and managing potential complications. Following tPA administration, BP should be closely monitored and kept $<180/105$ mm Hg; antithrombotic agents should be avoided for 24 h.

**Acute Stroke Treatment Within 3 to 6 h of Symptom Onset**

1.1.4. We do not recommend use of IV tPA for treatment of acute ischemic stroke of $>3$ h but $<6$ h in unselected patients (grade 2B). This treatment remains investigational.

1.1.5. We do not recommend that clinicians use streptokinase for the treatment of acute ischemic stroke except within the confines of a clinical trial (grade 1A).

1.1.6. In carefully selected 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 recommend the use intra-arterial thrombolytic therapy for ischemic stroke (grade 2B).

##### 1.2. Patients Not Eligible for Thrombolysis

**Remark:** To our knowledge, no trial has adequately evaluated full-dose anticoagulation in hyperacute ($<12$ h) stroke patients. Clinical trials evaluating IV heparin for stroke treatment are inconclusive with heterogeneous results. In general, trials of subcutaneous heparin and low-molecular-weight heparins or heparinoids have demonstrated an increase in the risk of major bleeding without any clear benefits.

1.2.1. We do not recommend full-dose anticoagulation for treatment of unselected patients with ischemic stroke (grade 2B)

1.2.2. Clinicians may consider early anticoagulation for treatment of acute cardioembolic and large-artery ischemic strokes and for progressing stroke when the suspected mechanism is ongoing thromboembolism (grade 2B).

**Remark:** Clinical trials have not adequately evaluated anticoagulation in specific stroke subtypes. For
patients with cardioembolic stroke, early anticoagulation is most likely to be beneficial for patients who are at high risk for early recurrent embolism (ie, patients with mechanical heart valves, an established intracardiac thrombus, atrial fibrillation associated with significant valvular disease, or severe congestive heart failure).

1.2.3. A brain imaging study should be performed prior to initiation of acute anticoagulation to exclude hemorrhage and estimate the size of the infarct. When potential contraindications to anticoagulation are present, such as a large infarction (based on clinical syndrome or brain imaging findings), uncontrolled hypertension, or other bleeding conditions, we recommend that clinicians avoid early anticoagulation (grade 1C).

1.2.4. We recommend early aspirin therapy (160 to 325 mg/d) for patients with ischemic stroke who are not receiving thrombolysis or anticoagulation (grade 1A). Aspirin therapy 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.

1.2.5. DVT/PE Prophylaxis: Because of the increased risk of PE and DVT among ischemic stroke patients, particularly in those with deficits leading to immobility, measures to reduce the risk of DVT and PE are required.

1.2.5.1. For acute stroke patients with restricted mobility, we recommend that clinicians use prophylactic low-dose subcutaneous heparin or low-molecular-weight heparins or the heparinoid danaparoid, as long as there are no contraindications to anticoagulation (grade 1A).

1.2.5.2. In patients with an intracerebral hematoma, we recommend that clinicians use low-dose subcutaneous heparin as early as the second day after the onset of the hemorrhage for the prevention of thromboembolic complications (grade 2C).

1.2.5.3. We recommend that clinicians use intermittent pneumatic compression devices or elastic stockings for patients who have contraindications to anticoagulants (grade 1C).

2. Stroke Prevention

2.1. Antiplatelet Agents

2.1.1. Noncardioembolic Cerebral Ischemic Events: We recommend that every patient who has experienced a noncardioembolic (atherothrombotic, lacunar, or cryptogenic) stroke or TIA and has no contraindication receives an antiplatelet agent regularly to reduce the risk of recurrent stroke and other vascular events. Aspirin, 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 (grade 1A).

2.1.2. The combination of aspirin, 25 mg, and extended-release dipyridamole, 200 mg bid, is more effective than aspirin alone for the prevention of stroke (grade 1A); and, based on indirect comparisons, the combination of aspirin, 25 mg, and extended-release dipyridamole, 200 mg bid, may be more effective than clopidogrel, 75 mg (grade 2C), and has a similarly favorable serious adverse effect profile.

2.1.3. For patients who are allergic to aspirin, we recommend clopidogrel in favor of ticlopidine (grade 2C).

2.2. Oral Anticoagulants

2.2.1. Inadequate data are available to evaluate the efficacy and safety of oral anticoagulants for prevention of noncardioembolic stroke. However, at INRs of 3.0 to 4.5, the risk of brain hemorrhage outweighs any potential benefit for stroke prevention. We recommend that clinicians do not treat with oral anticoagulation at INRs of 3.0 to 4.5 (grade 1A).

2.2.2. Cardioembolic Cerebral Ischemic Events: We recommend that clinicians use long-term oral anticoagulation (target INR of 2.5; range, 2.0 to 3.0) for prevention of stroke in atrial fibrillation patients who have suffered a recent stroke or TIA (grade 1A). 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). Inadequate clinical trial data are available to support specific recommendations for minor-risk cardiac sources. In general, we recommend antiplatelet agents for these patients (grade 2C).

2.2.3. Carotid Endarterectomy: We recommend that clinicians give aspirin, 81 to 325 mg/d, prior to carotid endarterectomy and following the procedure (grade 1A).

3. Cerebral Venous Sinus Thrombosis

3.1. Cerebral Venous Sinus Thrombosis

We recommend that clinicians use unfractionated heparin (grade 1A) or low-molecular-weight heparin (grade 1C) during the acute phase, even in the presence of hemorrhagic infarction caused by the sinus thrombosis, followed by oral anticoagulation for 3 to 6 months (target INR of 2.5; range, 2.0 to 3.0; grade 1C).

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