Advances in the Acute Treatment and Secondary Prevention of Stroke

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Stroke continues to be the leading cause of disability in industrialized nations and is one of the most difficult therapeutic challenges for physicians. Developments in neuroimaging and other diagnostic tests have improved our ability to identify and localize ischemic brain lesions and clarify their underlying etiologies. Until recently, however, physicians had no effective means of treating acute stroke. The success of thrombolytic therapy for acute stroke has invigorated clinical research aimed at identifying additional treatment options to expand and improve on intravenous thrombolysis. In the first part of this chapter, we focus on the large clinical trials of thrombolytic therapy for stroke and the clinical trial methodology that led to the success of the National Institutes of Neurologic Disorders and Stroke (NINDS) IV tPA trial.

Since most stroke patients are not eligible for acute treatment, improving our ability to prevent stroke remains of critical importance. The second part of this chapter highlights the developments of specific antihypertensive, lipid-lowering, and antiplatelet agents that have expanded our armamentarium to diminish stroke risk.

Looking to the future, we discuss the development of a new oral anticoagulant and ongoing challenges in the quest for a clinically effective neuroprotectant.

ACUTE TREATMENT: THROMBOLYTICS

The use of thrombolytic therapy for the treatment of acute ischemic stroke is the consequence of recent advances in clinical stroke trial design. The pivotal study from the NINDS recombinant tissue plasminogen activator (rt-PA) Stroke Study Group (1995) documented a significant benefit of IV rt-PA treatment of acute ischemic stroke within 3 hours of symptom onset. Based on this report, the U.S. Food and Drug Administration (FDA) approved rt-PA for the treatment of acute ischemic stroke within 3 hours of symptom onset.

Background

The investigation of thrombolytic agents for stroke treatment developed because the majority of ischemic strokes are caused by thrombotic or thromboembolic occlusions of cerebral vasculature. Without thrombolytic therapy, early spontaneous recanalization occurs in only a minority of patients (Del Zoppo et al., 1998; Kassem-Moussa and Graffagnino, 2002). Animal stroke models have demonstrated clot lysis with thrombolytic agents and improved neurological outcome following thrombolysis (Zivin et al., 1985; Del Zoppo et al., 1986). Initiation of human stroke trials was also encouraged by the success of streptokinase (SK) for the treatment of myocardial infarction first reported in 1988 in the Second International Study of Infarct Survival (ISIS-2) (1988).

Clinical Trials (Table 2.1)

Streptokinase

SK was studied for use in acute ischemic stroke in three large randomized trials that were conducted in Europe and Australia (Donnan et al., 1995, 1996). All three of the trials were terminated early because of safety concerns. The Multicenter Acute Stroke Trial-Italy
(MAST-I) (1995) and the MAST-Europe trial (1996) randomized patients to a fixed dose of SK within 6 hours of stroke onset, whereas the Australian Streptokinase Trial (ASK) (Donnan et al., 1996) randomized patients to a fixed dose of SK within 4 hours of onset. The fixed dose used in all three stroke trials was the same as that used for the treatment of myocardial infarction (MI). No studies designed to clarify the optimal dose of SK for stroke patients were undertaken before embarking on the large treatment trials. An indirect analysis using data from the MAST-E trial showed a trend for increased risk of early death in patients with lower body weight and thus a higher relative dose of SK (Cornu et al., 2000). This may be one explanation for the failed trials of SK treatment for stroke: The dose used may have been too high and was not adjusted for patient weight. SK is also frequently associated with hypotension when used for MI (10% of treated patients in ISIS-2 compared to 2% treated with placebo) and variably reported in stroke (20% of treated patients in the ASK trial, 1.9% in MAST-I, and 0.6% in MAST-E). In stroke patients acute hypotension could theoretically cause impaired blood flow to the ischemic penumbra, leading to poorer outcomes (Cornu et al., 2000). Finally, because SK has more prolonged fibrinogen depletion and anticoagulant effects compared to rt-PA, these differences may have contributed to the higher rates of hemorrhagic transformation (Cornu et al., 2000).

**Recombinant Tissue Plasminogen Activator (rt-PA)**

Multiple safety and feasibility studies investigating the potential use of rt-PA in acute stroke were conducted before the large-scale stroke trials (Brott et al., 1992; Haley et al., 1992). Based on dose-finding studies, a dose substantially less than that used for treatment of MI (0.9 mg/kg) was selected as the optimal dose for the large clinical trials.

The NINDS t-PA Stroke Study Group performed a randomized, double-blind, placebo-controlled trial of intravenous tPA for ischemic stroke within 3 hours of symptom onset (1995). A total of 624 patients were enrolled to receive either intravenous tPA 0.9 mg/kg (maximum 90 mg) or placebo. Therapy with tPA was initiated with a bolus (10% of the total dose) infused over 1 minute, and the remainder of the total dose infused over 60 minutes. A pretreatment computed tomography (CT) scan was required to exclude the presence of intracerebral hemorrhage (ICH). To minimize the risk of treatment-related ICH, strict inclusion and exclusion criteria were adhered to. After treatment, blood pressure was strictly maintained within prespecified values, and the use of antiplatelets and anticoagulants was not permitted for 24 hours.

The trial was conducted in two parts. Part 1 included 291 patients and was designed to assess the early clinical efficacy of tPA measured by an improvement in the National Institutes of Health Stroke Scale (NIHSS) score by four or more points or complete neurological recovery 24 hours after stroke onset. Part 2 included 333 patients and was designed to evaluate clinical outcomes at 3 months, focusing on the percentages of patients with minimal or no deficits.

In Part 1, no significant difference was detected in the percentages of patients with neurological improvement at 24 hours as previously defined. However, a secondary analysis did find significant improvement in median NIHSS scores among the tPA group.

In Part 2, the results of all outcome measures favored the tPA group. Benefits were consistent regardless of patient age, stroke subtype, and stroke severity. Treated patients were 30% more likely to have minimal or no disability at 3 months compared to placebo-treated patients.

**Reproduced from Albers et al. (2001). Antithrombotic and thrombolytic therapy for ischemic stroke, Chest 119:300-320.**

### TABLE 2.1 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>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>tPA %</td>
<td>Placebo %</td>
<td>tPA %</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo %</td>
<td></td>
<td>Death or Dependency OR (95% CI)</td>
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<tr>
<td>NINDS</td>
<td>624</td>
<td>0.9 (90)</td>
<td>≤ 3</td>
<td>6.4</td>
<td>0.6</td>
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<td>0.49 (0.35–0.69)</td>
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<tr>
<td>ECASS-I</td>
<td>620</td>
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<td>19.8*</td>
<td>6.5*</td>
<td>22</td>
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<td>15.6</td>
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<td>0.68 (0.55–0.95)</td>
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<tr>
<td>ECASS-II</td>
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<td>0.72 (0.55–0.95)</td>
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<tr>
<td>ATLANTIS-B</td>
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<td>0.9 (90)</td>
<td>3–5</td>
<td>7.0</td>
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<td>1.04 (—)</td>
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*Parenchymal hematoma (symptomatic ICH not reported in ECASS-I).
with an 11% to 13% absolute increase in the number of patients with excellent outcomes. Symptomatic ICH occurred in 6.4% of treated patients vs 0.6% for placebo ($P < .001$); however, there was no difference in mortality. The benefit of IV tPA seen at 3 months in the NINDS study was sustained over the long term. During a 12-month follow-up evaluation of these patients, the benefit of tPA over placebo remained virtually identical, with an 11% to 13% absolute increase in the number of patients achieving excellent outcomes (Kwiatkowski et al., 1999).

The European Cooperative Acute Stroke Study (ECASS) trial (Hacke et al., 1995) was a multicenter, double-blind, placebo-controlled trial that randomized 620 patients within 6 hours of stroke onset to treatment with IV tPA at a dose of 1.1 mg/kg (total dose limit 100 mg) or placebo. The protocol excluded patients with the most severe hemispheric stroke symptoms and patients with major early infarct signs on CT scan exceeding one third of the MCA territory. Primary outcome measures were the Barthel Index (BI) and modified Rankin Scale (mRS) at 3 months after treatment. Both an intention-to-treat (ITT) analysis and a target population (TP) (per-protocol) analysis were performed. A total of 109 patients were excluded from the TP analysis primarily because of the presence of extensive early ischemic changes on CT scan. There was no difference in BI scores at 3 months for either the ITT or TP groups. In the TP analysis, there was a significant difference in the mRS favoring tPA. There was no difference in mortality at 30 days; however, the incidence of parenchymal hemorrhages was significantly more frequent in the tP-treated patients (19.8% vs 6.5% in the placebo group). In an explanatory analysis of the ECASS data, advanced age was associated with an increased risk of parenchymal hemorrhage, while time-to-treatment was not related (Larrue et al., 1997). The initial clinical stroke severity and the presence of early ischemic changes on CT scan were associated with increased risk of hemorrhagic infarction. The investigators concluded that tPA may have a net benefit if patient selection could be improved to exclude patients at higher risk for complications, particularly those with major early infarct signs on CT scan.

The ECASS investigators also suggested that the higher dose of tPA used may have contributed to the increased hemorrhagic complications, a relationship supported by data from the myocardial infarction trials. Furthermore, strict blood pressure parameters were not included in this protocol. Therefore, ECASS II (Hacke et al., 1998) was designed with a lower dose of tPA (0.9 mg/kg to match the NINDS protocol) given within 6 hours of symptom onset, strict guidelines for blood pressure control, and strict adherence to CT criteria, including investigator participation in CT training courses before and during the course of the study. ECASS II also found no significant difference in the primary outcome (the percentage of patients with a favorable outcome [score 0 to 1] on mRS at 3 months). However, for the secondary post-hoc outcome of functional independence (score 0 to 2) on mRS, there was a significant difference in favor of tPA. Although there was a 2.5-fold increase in the symptomatic intracerebral hemorrhage rate for tPA-treated patients vs placebo, there was no difference in mortality. Patients in ECASS II had less severe strokes, with baseline median NIHSS scores of 11 in both groups, compared to 14 and 15 in the NINDS trial. This finding may account for the better outcomes in the ECASS II placebo group compared to the other tPA studies and may contribute to the lack of a substantial treatment effect on the primary outcome. Also, most patients (642 of 800) were treated in the 3- to 6-hour window, whereas in the NINDS trial, all patients were treated within 3 hours, and half within 90 minutes of stroke onset.

The Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) trial (Albers et al., 2002) had several similarities to ECASS II. The patients enrolled had milder strokes (median NIHSS score 11) and were treated at a later time (median time to treatment 4 hours 35 minutes) than the NINDS study. The ATLANTIS study design was similar to the NINDS study except for the time windows. ATLANTIS Part A began in 1991 with a 0- to 6-hour time window, which was changed in 1993 to 0 to 5 hours (Part B) because of safety concerns in the 5- to 6-hour window. There was no benefit in the treatment group for outcome measures at 3 months either for the target population treated in the 3- to 5-hour window or in the ITT analysis. However, a prespecified analysis of the 61 patients in ATLANTIS who were enrolled within 3 hours of stroke onset did find that the tPA-treated patients were more likely to have a very favorable outcome (NIHSS = 1) at 3 months ($P = .01$), supporting the conclusions of the NINDS study.

Primarily based on the success of the NINDS studies, in 1996 the FDA approved tPA for use in early acute ischemic stroke. After the publication of the NINDS trials, reports of clinical practice experience with IV tPA both in academic and community settings have demonstrated similar safety and clinical outcomes when the NINDS criteria were strictly used (Albers et al., 2000). The advent of an effective treatment for acute ischemic stroke has energized clinicians and spurred local and national stroke education campaigns. It has also stimulated ongoing research, including efforts to expand the therapeutic window of tPA using advanced neuroimaging techniques for patient selection, endovascular delivery of thrombolytics, and coupling of tPA with neuroprotective therapies.
STROKE PREVENTION

Treatment of Hypertension

The latest report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure emphasizes the need for more aggressive blood pressure (BP) control to prevent cardiovascular disease, including stroke (Chobanian et al., 2003). Normal BP is now defined as <120/80. For those 40 to 70 years old, each increment of 20 mm Hg in systolic BP or 10 mm Hg in diastolic BP doubles the risk of cardiovascular disease across the entire BP range from 115/75 to 185/115 (Lewington et al., 2002). To achieve adequate BP control, clinical trials have demonstrated that most patients will require two or more antihypertensive medications.

For primary and secondary stroke prevention, the effectiveness of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers has recently gained attention. Why have these particular classes of antihypertensives been of interest? There is both theoretical and clinical evidence to support the vascular and cardiac benefits of blocking the renin-angiotensin-aldosterone system (RAAS). This system controls systemic blood pressure through multiple mechanisms including modulation of the sympathetic nervous system, as well as direct effects on the heart, kidneys, and blood vessels (Weir and Henrich, 2000). The RAAS maintains salt and water homeostasis but may also promote chronic hypertension (Ruland and Gorelick, 2003). In this system, angiotensin I is converted to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II, a peptide hormone, has many vascular effects including vasoconstriction, inflammation, vascular remodeling, thrombosis, and plaque rupture primarily via activation of angiotensin II type 1 receptors (Schiffrin, 2002; McFarlane et al., 2003). Many of these effects are mediated via direct effects on endothelial cells and vascular smooth muscle cells. Angiotensin II and aldosterone increase the production of plasminogen activator inhibitor type 1 (PAI-1), the most important physiological inhibitor of tissue-type plasminogen activator (TPA) in plasma, and promote platelet aggregation (Lonn et al., 1994; Ruland and Gorelick, 2003). Angiotensin II is a major contributor to the generation of reactive oxygen species that oppose the vascular effects of nitric oxide, including the inhibition of the growth, remodeling, and migration of vascular smooth muscle cells, as well as the expression of proinflammatory molecules (McFarlane et al., 2003). Therefore, an imbalance between reactive oxygen species and nitric oxide leads to activation of endothelins (potent vasoconstrictors) and up regulation of proinflammatory mediators that contribute to vascular disease (Schiffrin, 2002).

The exact mechanisms by which ACE inhibitors may prevent vascular disease are not completely understood; however, multiple potential mechanisms have been hypothesized based on the actions of angiotensin II described previously (Figure 2.1). By blocking the conversion of angiotensin I to angiotensin II, ACE inhibitors may improve vascular compliance, reduce vascular smooth muscle proliferation, and have plaque-stabilizing as well as antithrombotic and antiinflammatory effects. They improve renal blood flow and reduce aldosterone secretion, thus reducing reabsorption of sodium (Ruland and Gorelick, 2003).

ACE inhibitors also prevent the breakdown of bradykinin, and it has been suggested that many of the known clinical benefits of ACE inhibitors may be to a large extent related to the increased concentrations of bradykinin in serum and possibly tissue (Weir and Henrich, 2000). Bradykinin is a powerful vasodilator that also secondarily augments the production of other vasodilators such as nitric oxide and cyclic GMP (Weir and Henrich, 2000). It causes a cascade of vasodilatory and antithrombotic effects. Human clinical studies have shown that plasma angiotensin II levels remain at or above pretreatment levels with chronic dosing of an ACE inhibitor, localizing the effects of ACE inhibitors perhaps to the vascular tissue (Weir and Henrich, 2000). Furthermore, it has been shown that a bradykinin receptor antagonist can inhibit the blood pressure-lowering effects of an ACE inhibitor, thus pointing to bradykinin as a potent mediator in the setting of ACE inhibitors (Weir and Henrich, 2000).

Angiotensin II acts via type 1 and type 2 receptors. The type 1 receptors mediate the known effects of angiotensin II. The current angiotensin receptor (AT₁) blockers specifically block these type 1 receptors (Schiffrin, 2002; McFarlane et al., 2003). There is evidence that the clinically observed benefits of AT₁ blockade may, to a large extent, be due to stimulation of the type 2 receptors, which are expressed more commonly in diseased and damaged tissues, rather than direct antagonism of the type 1 receptors (Weir and Henrich, 2000; Schiffrin, 2002). While the function of the type 2 receptors is less well defined, it appears to be antagonistic to type 1, thereby stimulating vasodilation via the bradykinin-nitric oxide-cyclic guanine monophosphate cascade as well as inhibiting smooth muscle cell proliferation and inflammatory responses (Weir and Henrich 2000; Schiffrin 2002).

There have been several recent large randomized trials that have demonstrated the effectiveness of ACE inhibitors or angiotensin receptor blockers (ARBs) in primary or secondary stroke prevention. Debate persists as to whether this benefit is due purely to the BP-lowering effect of these agents or to additional vascular protective effects described previously, which may be specific to these
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particular classes of antihypertensive agents (Anderson, 2003; Bath, 2003; Davis and Donnan, 2003).

The Heart Outcomes Prevention Evaluation (HOPE) (The Heart Outcomes Prevention Evaluation Study Investigators, 2000) was a double-blind, randomized, placebo-controlled trial of the use of an ACE inhibitor, ramipril, for the prevention of the composite outcome of MI, stroke, and cardiovascular death in high-risk cardiovascular disease patients. Of the 9541 patients randomized, 1013 had a previous stroke or transient ischemic attack. The mean BP at enrollment was 139/79. There was a 22% relative risk reduction (RRR) in the primary composite outcome. In fact, the study was terminated early because of the clear benefit of ramipril. There was also a 32% RRR of any stroke (3.4% vs 4.9% stroke incidence for ramipril and placebo, respectively) and a 61% RRR of fatal stroke (0.4% vs 1%) in the ramipril group (Bosch et al., 2002).

Despite these large cardiovascular outcome benefits, there was only a small reduction in BP (3/2 mm Hg) with treatment. Based on data derived from the World Health Organization and the International Society of Hypertension, the expected relative risk of MI and stroke from this small BP reduction would have been 5% and 13%, respectively, rather than the observed reductions of 20% and 32%, respectively (Sleight et al., 2001). Therefore, it has been hypothesized that much of the beneficial effect of ramipril on vascular events may be independent of its BP-lowering effect (Sleight et al., 2001). Alternatively, it has been suggested that the study’s daytime BP measurements may have underestimated the 24-hour BP reduction of ramipril, which was administered as a nighttime dose. A small substudy of HOPE monitored 38 patients with peripheral vascular disease who underwent 24-hour ambulatory BP (ABP) monitoring before randomization and after 1 year (Svensson et al., 2001). This substudy found that the 24-hour ABP was significantly reduced (10/4 mm Hg) primarily because of a more pronounced BP-lowering effect during nighttime (17/8 mm Hg). Therefore, the benefits of ramipril may be more attributable to the reduction in BP than previously concluded, although these findings are drawn from a very small sample size.

The benefit of BP lowering for reducing the risk of recurrent stroke was definitively shown in the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) (2001). This investigator-initiated trial was a double-blind, randomized, placebo-controlled study of the effects of a flexible BP-lowering regimen based on an ACE inhibitor (perindopril) with or without

![Figure 2.1: Mechanisms of action of ACE inhibitors and angiotensin II receptor subtype 1 blockers. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.](image-url)
the addition of a diuretic (indapamide) on the primary outcome of total stroke (fatal or nonfatal). Of the 6105 patients enrolled, there was a 28% RRR for recurrent stroke for those assigned active treatment over placebo (10% vs 14% stroke incidence). The overall reduction in recurrent stroke risk was comparable to the reduction in primarily initial stroke risk seen in the HOPE study (32%) and included reduction in the outcome endpoints of nonfatal or disabling stroke (24%), ischemic stroke (24%), and cerebral hemorrhage (50%). Combination therapy with perindopril plus indapamide reduced BP by 12/5 mm Hg and stroke risk by 43%, whereas perindopril alone reduced BP by 5/3 mm Hg and had no significant effect on stroke risk. There were similar benefits for both the hypertensive and nonhypertensive subgroups, although hypertension was defined as a systolic BP >160 or a diastolic BP >90 at baseline, a cutoff level quite high compared with current guidelines of 120/80 (Chobanian et al., 2003). The mean baseline BP of those classified as hypertensive was 159/94 mm Hg and for the nonhypertensive was 137/79 mm Hg. In addition to the stroke risk reduction, there was a 26% reduction in major vascular events including a 38% reduction in nonfatal MI.

Combination therapy of perindopril plus indapamide clearly resulted in larger BP reductions and larger risk reductions than perindopril alone. PROGRESS demonstrated that aggressive BP lowering can significantly reduce the risk of recurrent stroke and major vascular events, even in patients who may already be treated with other stroke prevention therapy such as antiplatelets or anticoagulants. It was not designed, however, to test for potential benefits of the ACE inhibitor independent of its BP-lowering effect, as the study was powered to detect a 30% reduction in total stroke risk among those receiving active treatment over placebo.

While PROGRESS did not seek to establish a benefit of the ACE inhibitor perindopril beyond its BP-lowering effect, the Losartan Intervention for Endpoint reduction (LIFE) trial (Dahlof et al., 2002) did aim to determine whether the ARB, losartan, had cardiovascular benefits independent of BP-lowering. LIFE was an investigator-initiated, double-blind, randomized, controlled trial of losartan (the first angiotensin II type 1 receptor blocker) vs atenolol in patients with hypertension and left ventricular hypertrophy for the prevention of cardiovascular morbidity and death. Atenolol was chosen as the comparator because it was recognized worldwide as a first-line treatment for hypertension with similar antihypertensive efficacy to losartan. Hydrochlorothiazide and additional antihypertensive agents (except ACE inhibitors, ARBs, and β-blockers) could be added to the blinded study medications if needed to achieve a goal BP <140/90. Blood pressures were reduced substantially in both groups (by 30.2/16.6 and 29.1/16.8 mm Hg in the losartan and atenolol groups, respectively). There was equal use of additional antihypertensive agents between the two groups. During a mean follow-up period of 4.8 years, there was a 13% RRR for the primary composite endpoint of cardiovascular death, MI, and stroke for losartan over atenolol. Furthermore, there was a 25% RRR for stroke for losartan-treated patients; of the 9193 subjects who participated, 232 losartan patients and 309 atenolol patients experienced a stroke. There were fewer MIs than strokes in both groups and no difference in the incidence of MI between the two groups. There was a very small difference between groups in systolic and diastolic blood pressures but not in mean arterial pressure. Adjustment of the primary outcome for changes in systolic, diastolic, or mean arterial pressure did not appreciably affect the outcome results. Therefore, the cardiovascular benefit, and particularly the stroke benefit, seen with losartan over atenolol supports a BP-independent effect of this angiotensin II type 1 receptor blocker in high-risk hypertensive patients.

Treatment of Hypercholesterolemia

Although epidemiological studies have not established as clear a link between serum cholesterol and stroke as they have for cholesterol and MI (Thomas et al., 1966), this failure may be due to several study limitations. A meta-analysis of 45 prospective observational cohorts, including 450,000 subjects and 13,000 strokes, found no association between total cholesterol and stroke (1995). The Multiple Risk Factor Intervention Trial (MRFIT) (Iso et al., 1989) did find a positive association between serum cholesterol levels and death from nonhemorrhagic stroke in men 35 to 57 years old, but also found a negative association between intracranial hemorrhage and serum cholesterol levels <160 mg/dl (4.1 mmol/L) in hypertensive men. Several possible explanations have been proposed for why the observational studies to date have failed to show a clear association between cholesterol and stroke. The primary limitation of these studies has been that the cohorts of patients have not been representative of the population at risk for ischemic stroke (Amarenco, 2001). The studies focused on middle-aged subjects at risk for MI, when the incidence of stroke is known to rise one to two decades later than coronary heart disease (CHD). When strokes do occur in this younger population, the cause is less likely due to atherothrombosis and instead is more commonly due to causes unrelated to cholesterol such as heart valve disease or carotid/vertebral artery dissection. In many studies the strokes were not differentiated by subtype to possibly detect an association between cholesterol and ischemic atherothrombotic strokes separated from hemorrhagic or cardioembolic strokes (Amarenco, 2001).
Despite the lack of epidemiological evidence to confirm cholesterol as a marker for stroke risk, several landmark trials have demonstrated a beneficial effect of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors ("statins") in reducing stroke risk in patients with CHD. Statins inhibit the rate-limiting enzyme in cholesterol biosynthesis. By inhibiting this enzyme, statins lead to an up regulation in the expression of low-density lipoprotein (LDL) receptors on hepatocytes and therefore enhanced clearance of circulating LDL (Hess et al., 2000). However, beyond lowering serum cholesterol levels, statins possess additional mechanisms of action that may contribute to their beneficial effects in stroke and may be independent of cholesterol-lowering effects (Table 2.2). Statins have antithrombotic effects by blocking platelet activation and increasing endothelial cell fibrinolytic activity. They have anti-inflammatory effects by blocking macrophages, reducing matrix metalloprotease secretion, lowering levels of C-reactive protein, and inhibiting the activation of inflammatory cytokines. Furthermore, they decrease smooth muscle cell migration and proliferation and, in vitro, induce vascular smooth muscle cell apoptosis, which may be one of the mechanisms by which statins reduce intima-media wall thickness in patients with carotid atherosclerosis (Hess et al., 2000).

A meta-analysis of the 13 randomized, placebo-controlled, double-blind trials of statins reporting on stroke from 1980 to 1996 found an overall stroke risk reduction of 31% (Blauw et al., 1997). The mean age in these trials ranged from 55 to 68 years. This analysis included the Scandinavian Simvastatin Survival Study (4S) (1994) in which 4444 patients with CHD and a mean total cholesterol of 263 mg/dl were randomized to simvastatin or placebo. In a post-hoc analysis, there was found to be a 28% RRR for fatal and nonfatal strokes or transient ischemic attacks (Pedersen et al., 1998). The meta-analysis also included the Cholesterol and Recurrent Events (CARE) trial (Sacks et al., 1996), which was a randomized, controlled trial of pravastatin in 4159 patients with recent MI and average cholesterol levels (mean total cholesterol 209 mg/dl, mean LDL 139 mg/dl). The treatment group had a 31% RRR (incidence 2.6% vs 3.8%) of stroke, a prespecified endpoint of the trial. There was a treatment-associated reduction across all stroke subtypes, although there was a small number of outcome events in each subtype (Plehn et al., 1999). There was also no increase in intracerebral hemorrhages with pravastatin, although there were only eight hemorrhagic events (Plehn et al., 1999).

The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) study (The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group, 1998) was published after the previously mentioned meta-analysis but supported the findings of both the meta-analysis and the 4S and CARE trials. LIPID was a randomized, controlled trial of pravastatin in 9014 patients with CHD, with a somewhat broader range of total cholesterol levels (range 155 to 271 mg/dl). There was a 19% RRR for total stroke, with a 23% RRR for ischemic stroke (incidence 3.4% vs 4.4%) and a consistent effect across all ischemic stroke subtypes. Again, there was no increase in intracerebral hemorrhage, although the total number of hemorrhagic events (28) was too small to draw any conclusions (White et al., 2000).

The most recent clinical evidence establishing the benefit of lipid modification for stroke prevention in high-risk patients is the Heart Protection Study (2002), which reported its results of a randomized, controlled trial of simvastatin in 20,536 patients with vascular risk factors. This study further established that there are benefits irrespective of initial cholesterol concentrations. Subjects included men and women 40 to 80 years old (28% older than age 70) with total cholesterol ≥135 mg/dl (3.5 mmol/L), and a history of CHD, other occlusive arterial disease, or diabetes. There was a 25% RRR (4.3% vs 5.7%) for first stroke, primarily resulting from a 30% RRR in ischemic stroke (2.8% vs 4%). There was no difference in the incidence of hemorrhagic strokes, with a total of 104 hemorrhagic stroke events. Because approximately one sixth of the treatment group stopped taking statin therapy and one sixth of the placebo group initiated a statin during the study, the ITT analysis actually reflects the effects of about two thirds of the treated group actually taking simvastatin. Therefore, the actual reduction in stroke rate may be greater than the 25% RRR seen in the study. Furthermore, this benefit was additive to the other preventive treatments continued during the study including antplatelet and antihypertensive agents.

<table>
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<th>TABLE 2.2 Beneficial Effects of Statin Agents</th>
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<tr>
<td>Lipid-modifying</td>
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<td>↓LDL</td>
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<tr>
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<tr>
<td>Block platelet activation</td>
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<tr>
<td>↑Endothelial cell fibrinolytic activity</td>
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<td>Anti-inflammatory</td>
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<tr>
<td>Block macrophages</td>
</tr>
<tr>
<td>↓Matrix metalloprotease secretion</td>
</tr>
<tr>
<td>↓Decrease C-reactive protein</td>
</tr>
<tr>
<td>Inhibit inflammatory cytokine activation</td>
</tr>
<tr>
<td>Vasomotor</td>
</tr>
<tr>
<td>↓Smooth muscle cell migration and proliferation</td>
</tr>
<tr>
<td>Induces vascular smooth muscle cell apoptosis</td>
</tr>
<tr>
<td>→decrease intima-media wall thickness</td>
</tr>
</tbody>
</table>

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The proportional reduction in LDL with statin treatment in the Heart Protection Study was independent of initial cholesterol level. There was also no lower threshold seen below which lowering cholesterol did not reduce risk. Even among subjects with “normal” LDL levels of <100 mg/dl (2.6 mmol/L), reducing the average LDL to 65 mg/dl (1.7 mmol/L) in the treated group was safe and resulted in a risk reduction similar to those with higher LDL levels.

These large clinical trials definitively establish that middle-aged and older high-risk patients achieve substantial benefit in ischemic stroke risk reduction with statin therapy, specifically pravastatin and simvastatin, even with normal or moderate baseline cholesterol levels. Based on these studies, statins do not appear to increase hemorrhagic stroke incidence, although the total number of observed hemorrhagic events has been small. Most of these studies have focused on patients with CHD rather than those with primarily cerebrovascular disease. The Stroke Prevention by Aggressive Reduction of Cholesterol Levels (SPARCL) trial (Amarenco, 1999) has been designed to determine whether aggressive cholesterol-lowering therapy with atorvastatin, 80 mg, can reduce the incidence of stroke in patients without CHD but with a history of stroke or transient ischemic attack. This first prospective study of statins in secondary stroke prevention is currently ongoing.

A neuroprotective mechanism of statins has been described (Endres et al., 1998). Mediated by up regulation of endothelial nitric oxide synthase rather than by the decrease in cholesterol levels, infarct size in mice with normal cholesterol levels who were pretreated with simvastatin was significantly reduced. This protection may be related to enhanced blood flow or inhibition of platelet aggregation or leukocyte adhesion, all known nitric oxide-mediated effects. The prophylactic use of statins to decrease the severity of ischemic injury deserves further investigation.

**Antiplatelet Therapy: Dipyridamole**

In the quest to improve the effectiveness of antiplatelet therapy beyond aspirin in secondary stroke prevention, dipyridamole has been investigated alone and in combination with aspirin. It was initially thought that the antithrombotic effects of dipyridamole were purely platelet-mediated via phosphodiesterase inhibition. However, early platelet aggregometry studies, which separated platelets from other blood cells, showed only weak antiplatelet effects of dipyridamole (Eisert, 2001a, 2001b). The development of whole-blood impedance aggregometry, which better approximates in vivo thrombus formation, demonstrated that dipyridamole inhibits platelet aggregation more effectively in whole blood than in platelet-rich plasma. This suggested that dipyridamole had additional antithrombotic mechanisms beyond its direct antiplatelet effects. Other newer laboratory techniques have corroborated this hypothesis. A process was developed to create a subendothelial matrix covered with endothelial cells to simulate the vascular environment. With this model, dipyridamole has been found to enhance the indirect (near-field) antithrombotic action of the endothelium through multiple possible mechanisms (Eisert, 2001a, 2001b). These mechanisms include the inhibition of the uptake of adenosine, a potent endogenous inhibitor of platelet aggregation; potentiation of endogenous prostacyclin, a potent antithrombotic substance released from the vessel wall; and enhancement of endothelium-derived relaxing factor or nitric oxide, an inhibitor of platelet aggregation and adhesion as well as a vasodilator (Eisert, 2001a and b). Dipyridamole also has antioxidant properties that may contribute to its benefit in atherosclerosis (Eisert, 2001b) (Figure 2.2).

Early clinical studies of dipyridamole as an antiplatelet agent were discouraging. The Antiplatelet Trialists’ Collaboration (1994) performed a meta-analysis of 14 trials that compared the combination of dipyridamole and aspirin vs aspirin alone for prevention of nonfatal stroke, nonfatal MI, or vascular death. They found that dipyridamole provided no additional reduction in vascular events (316/2661 with aspirin plus dipyridamole vs 312/2656 with aspirin alone), but they concluded that a moderate difference had not been excluded by the studies. The European Stroke Prevention Study (ESPS-1) compared aspirin (325 mg three times a day) plus dipyridamole standard-release formulation (75 mg three times a day) with placebo in patients with previous transient ischemic attack (TIA) or stroke and demonstrated a 38% relative risk reduction of recurrent stroke (33% RRR in stroke or death) (ESPS-1, 1987). However, ESPS-1 did not compare the combination of dipyridamole plus aspirin to aspirin alone. The results of ESPS-2, reported in 1996, were consistent with ESPS-1 and it was the first study to demonstrate a significant benefit of dipyridamole plus aspirin over aspirin alone (Diener et al., 1996). It was a randomized, placebo-controlled, double-blind trial involving 6602 patients with prior TIA or stroke within the preceding three months. It compared aspirin (25 mg twice a day) plus modified-release dipyridamole (200 mg twice a day) to each medication alone and to placebo. The combination of dipyridamole plus aspirin achieved a 37% RRR in recurrent stroke over placebo and a 23% RRR in recurrent stroke (3% absolute risk reduction) over aspirin alone. Why was the ESPS-2 trial able to demonstrate a significant benefit of combination therapy
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dipyridamole plus aspirin while the previous 14 trials analyzed by the Antiplatelet Trialists’ Collaboration had not? One important factor may be the limited number of events captured in those earlier trials: 142 nonfatal strokes compared to the 323 nonfatal strokes in ESPS-2 alone (Wilterdink and Easton, 1999). Furthermore, the Antiplatelet Trialists’ Collaboration compared the reduction in combined vascular events (stroke, MI, and vascular death). When one excludes the trials in which no strokes occurred or in which stroke outcomes were not studied, data from the remaining nine trials combined favor dipyridamole plus aspirin over aspirin alone for prevention of nonfatal stroke, although results were not statistically significant (Wilterdink and Easton, 1999). The total number of nonfatal strokes in the other nine trials was 142; therefore, the 323 strokes in ESPS-2 provides more than twice as much outcome data as those previous nine trials combined. ESPS-2 was the only one of the trials discussed to use the sustained-release formulation, which provides better absorption of dipyridamole and allows twice-a-day (rather than three to four times per day) dosing.

**FUTURE DIRECTIONS**

**Direct Thrombin Inhibitors**

With respect to oral anticoagulation therapy, the armamentarium to date has been limited to warfarin and related vitamin K antagonists, which limit the synthesis of γ-glutamyl carboxylated forms of coagulation factors, factors II, VII, IX, X, protein C, and protein S, thereby impairing their function (Elg et al., 1999). Clinicians are intimately familiar with the limitations of warfarin including its narrow therapeutic window—a doubling of the dose of warfarin in an arterial thrombosis model in rats increased the antithrombotic effect of warfarin from 23% to 81%—and its large individual patient variability in effect, necessitating close monitoring and dose adjustments.
Warfarin also has a delayed onset of action dependent on the turnover rate of the coagulation factors and numerous food and drug interactions.

Low-molecular-weight direct thrombin inhibitors (e.g., melagatran and inogatran) are under investigation as alternative oral anticoagulants. These agents are direct inhibitors of thrombin; therefore, they inhibit only one factor in the coagulation cascade, the final common pathway for fibrin formation. A rat arterial thrombosis model demonstrated shallow dose- and plasma concentration-response curves for the direct thrombin inhibitors (for the purposes of the experiment they were administered as continuous infusions) vs the steeper curve for warfarin. It has been suggested that the dose-response curves for each individual factor will superimpose on each other, resulting in a steeper dose-response curve and thus the narrow therapeutic window exhibited by warfarin (Elg et al., 1999).

Bleeding complications are a constant concern in the clinical use of anticoagulants. A tail transection bleeding time experiment in a rat model showed significant prolongation of the bleeding time for heparin and warfarin at the doses necessary to achieve an 80% antithrombotic effect, while melagatran did not prolong the bleeding time (Elg et al., 1999). Bleeding time for melagatran did not increase until twice the dose necessary to achieve an 80% antithrombotic effect, suggesting a wider therapeutic window. With regard to laboratory assays, there was little prolongation of activated prothrombin time and prothrombin time with melagatran treatment in the rat model despite therapeutic antithrombotic effect. Instead, thrombin time was the assay prolonged in a dose-dependent manner with melagatran treatment.

With parenteral or oral administration of melagatran, therapeutic effect is achieved within minutes to hours (Bredberg, 1999). Whereas parenteral administration provides complete bioavailability and low variability, oral administration does not. To overcome this obstacle and optimize the gastrointestinal absorption of melagatran, the first prodrug direct thrombin inhibitor was developed (Gustafsson et al., 2001). The prodrug is uncharged at intestinal pH and 170 times more lipophilic than melagatran and, as a result, has much greater bioavailability and lower variability; therefore, the pharmacodynamic benefits of melagatran are preserved. In addition, the minimal antithrombin effects of the prodrug against thrombin should decrease the risk of major bleeding in patients with undiagnosed gastrointestinal bleeding (Gustafsson et al., 2001).

The melagatran prodrug, called ximelagatran, is currently being investigated in two long-term Phase III human clinical trials for stroke prevention (SPORTIF III and V: Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation) (Halperin, 2003b). Enrolled patients have atrial fibrillation and at least one additional risk factor for stroke. SPORTIF III is a randomized, open-label, parallel-group study with blinded event assessment involving 3407 patients in 23 countries; SPORTIF V is similar but with double-blind treatment allocation involving 3922 patients in North America. Given the established impressive efficacy of warfarin in stroke prevention in patients with nonvalvular atrial fibrillation (68% relative risk reduction in one meta-analysis) (Atrial Fibrillation Investigators, 1994), the objective of the phase III SPORTIF trials is to establish the noninferiority of ximelagatran relative to warfarin in this patient population. The safety and efficacy of fixed-dose ximelagatran (36 mg twice a day) are being compared with dose-adjusted warfarin (INR 2.0-3.0) with the primary endpoint being the incidence of all strokes and systemic embolic events.

Results of SPORTIF III were recently presented (Halperin 2003a). In the ITT analysis, 56 primary events occurred in the warfarin group (2.3% per year) and 40 occurred in the ximelagatran group (1.6% per year). This relative risk reduction of 29% and absolute risk reduction of 0.7% per year showed ximelagatran’s noninferiority relative to warfarin. There was also no significant difference between the two agents in the event rate for intracranial hemorrhage or major bleeding. Results of SPORTIF V have not yet been reported. Should they confirm the findings of SPORTIF III, one would anticipate that ximelagatran will become first-line treatment for stroke prevention in patients with atrial fibrillation.

Neuroprotectives

Despite the available antiplatelet, antihypertensive, and lipid-lowering agents for stroke prevention, as well as thrombolytic therapy for acute stroke treatment, minimizing ischemic injury during a stroke remains an important challenge. Although several neuroprotective drugs have been successfully developed in stroke animal models (Sydserff et al., 1995; Lesage et al., 1996), human clinical trials have been disappointing. What lessons can be learned from the shortcomings of the negative clinical trials when designing future neuroprotective trials?

Time Window

Although animal studies have involved drug administration before or soon after the onset of ischemia, none of the clinical trials published between 1995 and 1999 enrolled patients within 3 hours of symptom onset (Kidwell et al., 2001). In fact, the median time to entry was 12 hours, with a median time to treatment of 14 hours. To maximize the chances for detecting a treatment benefit, the time window should be as soon as possible after stroke onset and should reflect data from preclinical models.
Dose and Duration

As with the selection of time window, the drug dose chosen should reflect data from the preclinical and preliminary human studies. In some instances, the dose of a neuroprotective drug found to be effective in animals may be associated with adverse effects in clinical application. This can lead to suboptimal dosing to avoid even potentially acceptable side effects and result in a negative clinical trial (De Keyser et al., 1999). In general, Phase II trials have been inadequately designed to determine the most likely effective and safe doses to focus on in Phase III trials. Optimal duration of treatment for neuroprotective drugs is also not well established. Side effects can limit treatment duration. Based on evidence such as the prolonged elevation of excitatory amino acids after stroke in some patients (Bullock et al., 1995) and magnetic resonance spectroscopy suggesting ongoing neuronal loss over many days after stroke (Saunders et al., 2002), an extended treatment duration may be required (Gladstone et al., 2002). Certain drugs such as NMDA antagonists, benzodiazepines, or barbiturates may be beneficial if given early after ischemia but may impair recovery if given late (Gladstone et al., 2002). This issue will need to be addressed on an individual drug or drug class basis.

Stroke Standardization

Animal stroke models usually involve young, healthy animals with a middle cerebral artery occlusion, while neuroprotective clinical trials have typically enrolled a variety of stroke subtypes of varying severity (Gladstone et al., 2002). Depending on the mechanism of action, some drugs may have more of an effect on cortical than on white matter infarcts, or vice versa. Furthermore, in strokes in certain territories and of an intermediate severity, one may be more likely to be able to detect and measure benefit (Gladstone et al., 2002; Grotta, 2002). Perhaps the use of advanced neuroimaging techniques such as magnetic resonance diffusion and perfusion-weighted imaging can be used to identify patients who are most likely to benefit from acute stroke therapies.

Combination Therapies

Most likely the future use of neuroprotective drugs in acute ischemic stroke will be in the setting of combination therapy, such as two neuroprotective agents with synergistic mechanisms of action, the use of thrombolytic therapy preceded and/or followed by neuroprotection, the use of two or more agents during different therapeutic windows, or the use of a neuroprotective with nonpharmacological interventions such as hypothermia (De Keyser et al., 1999; Gladstone et al., 2002; Grotta, 2002). Although these trials will require increased complexity in design and conduct, they offer the potential to demonstrate efficacy with lower drug doses and therefore decreased toxicity and adverse effects.

CONCLUSIONS

We have illustrated the developments of several recent advances in acute stroke treatment and secondary stroke prevention. Clearly, the ability to effectively treat a patient having an acute stroke and reverse the neurological deficit can be dramatic and rewarding. The use of IV tPA has empowered physicians when they encounter eligible stroke patients. To expand our treatment abilities, many avenues remain open for exploration including neuroimaging for patient selection, neurointerventional techniques, and neuroprotectants. To diminish stroke risk, aggressive control of traditional risk factors continues to be the key element, and it is in the treatment of these risk factors that we are elucidating some of the mechanisms underlying cerebrovascular disease such as inflammation. Elucidating mechanisms that allow traditional therapies, such as antihypertensives and cholesterol-lowering agents to provide additional vascular protective effects will lead to the development of more effective pharmacological agents. Continued clinical investigations will enable us to build on our current successes treating and preventing stroke and its long-term effects.

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