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REVIEW

Stroke—Incidence, Mortality, Morbidity and Risk

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In the United States, 700,000 strokes, responsible for 165,000 deaths, occur each year. Worldwide, stroke is the 2nd leading cause of death. Stroke is a major health problem; and as the population ages, its significance will grow. This paper reviews the epidemiology of stroke, the identification of modifiable risk factors, and some of the options for intervention that can reduce stroke-related mortality and morbidity. Though the diagnosis and care of stroke patients has improved, mortality resultant from stroke remains significant, with only 50% 5-year survival in some clinical studies. The risk of stroke following a transient ischemic attack (TIA) or initial stroke is also significant—approximately 30% following either event. Stroke severity at onset and patient age are the most important factors for predicting prognosis.

Stroke prevention focuses on management of the traditional cardiovascular risk factors especially control of blood pressure and smoking cessation. The role of diabetes and lipid control in stroke prevention continues to be studied. The optimum use of anticoagulation to reduce stroke risk has been explored by the Stroke in Patients with Atrial Fibrillation (SPAF) studies. Carotid endarterectomy is effective in stroke prevention for those with symptomatic carotid obstruction of 70%, but its role in other scenarios is less certain. Antiplatelet drugs continue to be an important therapy for the prevention of recurrent stroke. Centralized stroke centers that specialize in stroke diagnosis and care along with rapidly rendering appropriate treatment can improve mortality and morbidity of stroke by 20%.

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OVERVIEW

There are 700,000 strokes, both incident (500,000) and recurrent (200,000), in the United States each year.[1] There are approximately 165,000 stroke-related deaths each year, and there are more than 4.5 million survivors of stroke, of whom more than a million have significant residual disability. Worldwide, stroke is the 2nd leading cause of death. Stroke is a major health problem; and as the population ages, its significance will grow.

After heart attack and cancer, stroke is the 3rd leading cause of death in the United States. This mirrors causes of death in most Western countries where approximately 50% of deaths are attributed to vascular disease.

The total cost of stroke is enormous. Based on data from the American Stroke Association (a division of the American Heart Association), stroke costs approximately $50 billion a year to the US economy—$31 billion in direct costs and about $20 billion in indirect

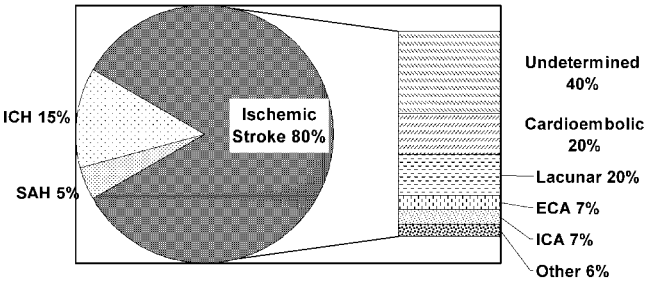

Figure 1. *Causes of Stroke.[1] 80% of all strokes are ischemic, 20% are hemorrhagic. Of the latter, 15% are intracerebral hemorrhage (ICH) and 5% are subarachnoid hemorrhage (SAH). Underlying types/causes of ischemic stroke are shown in the bar graph at the right. ECA = extracranial carotid artery disease. ICA = intracranial carotid artery disease.*

costs. This is a large economic burden on society, not to mention the personal burden of caring for stroke survivors with significant disability.

CAUSES OF STROKE

Among the total population of stroke patients, about 20% have hemorrhagic stroke. Three out of four hemorrhagic strokes are intracerebral hemorrhages, while the rest are subarachnoid hemorrhages. The latter represent 5% of all strokes. The remaining 80% of strokes are ischemic, as shown in Figure 1. Cardio-embolic and lacunar stroke are the most commonly identified causes of ischemic stroke representing approximately 20% of ischemic strokes each. Extracranial carotid disease (ECA) and intracranial carotid disease (ICA) make up about 7% each. A high percentage (40%) of strokes have no identified cause, which is frustrating to patients, clinicians and researchers. As our ability to investigate the causes of stroke improves, these proportions will change. Optimal stroke management and secondary prevention depends on the ability to determine the underlying cause.

STROKE EPIDEMIOLOGY

Incidence and Prevalence

Stroke incidence increases with age.[2] The incidence is higher in men, but the prevalence of stroke is higher in women because there are more women in the population, especially over the age of 70 years.[2] Stroke represents a very significant burden in women with respect to health morbidity. Based on epidemiologic studies in Cincinnati, Ohio, and Northern Manhattan, NY, the incidence of stroke is higher in the black and Hispanic populations.[3–5] These studies also found a higher incidence of intracerebral hemorrhage in these ethnic groups and a higher incidence of lacunar stroke in the Hispanic population.

The only available longitudinal data concerning stroke incidence for the US population comes from Rochester, Minn. The Olmsted County population based Epidemiology Project has run since the 1950s. A significant limitation is that the Olmsted County population is only about 110,000; and the city of Rochester has a population of approximately 80,000. The Olmstead County stroke registry has access to records from the Mayo Clinic as well as other medical clinics and private practices in the county.

The most recent stroke incidence data for the Rochester population is from the late 1980s. In the 1984–1989 period, the age- and sex-adjusted incidence for stroke overall was 145/100,000 population.[2] The adjustment procedure used the 1970 US white population as its basis, since Olmsted County is predominately Caucasian. Thus, while there are some limitations in interpreting the data in Rochester, it is thought that it reflects stroke incidence trends overall in the country. Because the Rochester study is limited to the evaluation of a population of 80,000 people, the actual number of events is relatively small, so the event rates are computed as running 3-year averages to assess longitudinal trends in stroke incidence.

As we can see in Figure 2 from 1955 onwards into the late 1970s, there was a significant and continual decline in stroke incidence thought to be due predominantly to better recognition and treatment of hypertension.[6] After the decrease in the late 1970s and early 1980s, there was an increase in incidence in the late 1980s. Data from other coun-

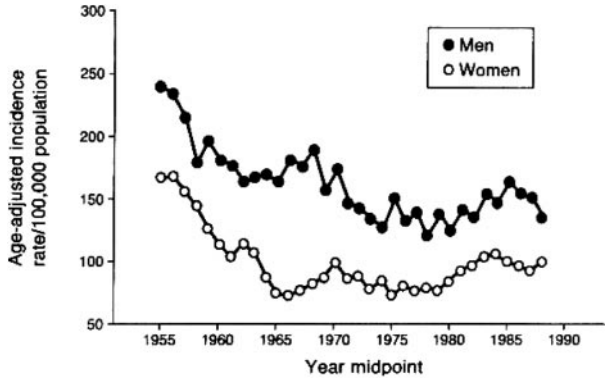

Figure 2. *Age-adjusted incidence of stroke for men and women in the Rochester, Minn population.[2] Running 3-year averages from 1955 to 1989. From: Brown et al,* Stroke, *1996. Permission to reprint granted by Lippincott Williams & Wilkins.*

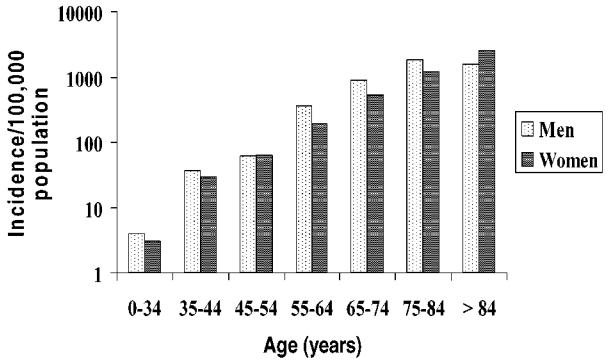

Figure 3. *Age-specific incidence of stroke for men and women in the Rochester, Minn, population for the period 1985–1989.[2] From: Brown et al,* Stroke, *1996. Permission to reprint granted by Lippincott Williams & Wilkins.*

tries with population-based epidemiologic surveillance systems such as Sweden indicate similar trends. The reason for this trend is not clear, however, most of the increase in stroke incidence in Rochester, Minn, occurred in patients who survived a heart attack or were diagnosed with ischemic heart disease.[7] In other words, incident strokes occurred in patients with ischemic heart disease who survived long enough so they could have a stroke. This fits our knowledge of the natural history of atherosclerotic cardiovascular disease. The average age of onset of ischemic heart disease is about 10 years earlier than cerebral vascular disease.

Another possible reason for the upswing in stroke incidence is that beneficial effects of anti-hypertension medications could ''wear off'' after chronic use. This hypothesis is as yet unproven. By the late 1980s, the study of vascular event rates in cohorts and populations included the evaluation of hypertensive individuals who had been treated for 20 years or more. With the development of MRI scanning, we know that many hypertensive patients have both symptomatic and asymptomatic white matter disease and small strokes; but whether the prevalence of these findings has changed over time is unknown. However, I believe it is likely that blood pressure can only be treated for so long before consequences occur. For the most part, studies of hypertension treatment and stroke have looked at the event rate primarily in the early period of treatment, 1–2 years after diagnosis. As far as I am aware, we have neither longitudinal data nor long-term studies of vascular event rates among individuals who have had blood pressure treated for 20 years or more.

The age-specific incidence of stroke for men and women from the Rochester, Minn, study for the 1985–1989 time period[2] is shown in Figure 3. Caution should be used when interpreting the incidence rates for the very old because of small numbers of these individuals in the population. But consistently across age groups, men have a slightly higher incidence rate than women.

When stroke type is considered, most of the change in stroke incidence over 1950–1989 occurred because of reduction in the incidence of cerebral infarction. The incidence rates of cerebral hemorrhage and subarachnoid hemorrhage were fairly stable over this interval. There was a slight increase in the incidence of intracerebral hemorrhages in the last period 1980–89, partly due to reclassification of stroke cause with the routine use of computerized tomography (CT) scan rather than clinical diagnostic criteria. Stroke prevalence is always higher than the incidence, and in this population it's about 6 to 7 times higher than the incidence.[2]

Stroke Mortality

Stroke is not only associated with significant morbidity but also with high mortality.

To summarize the CDC data among US residents in 1999, there were 167,000 stroke-related deaths with an age-adjusted rate of 63.4 per 100,000 (using 2000 US population for age adjustment).[8] With 500,000 incident strokes and 167,000 stroke-related deaths per year, the mortality rate is about one third among those who have an incident stroke.

Clinically, we use the rule of ''thirds'' as a guide: one third of patients who have a stroke recover, either completely or with minimal residual disability; one third recover with residual disability; and about one third die. The mortality of stroke is higher in the black population than in the white population. There is no difference in stroke mortality between men and women within each ethnic group. Not unexpectedly, stroke mortality increases with age, with many studies demonstrating an exponential increase in the stroke death rate with increasing age.

The period of highest mortality is within the first 30 days, with some variation by stroke subtype.[1] Approximately 10% of subarachnoid hemorrhage patients die before they receive medical attention.[9] There is a very high fatality rate in subarachnoid hemorrhage in the first 1–2 days.[9] This is in contrast to cerebral infarction where deaths begin to occur a few days to a few weeks after onset.[10] Many stroke patients experience pneumonia, pulmonary embolism, or other problems that lead to death.

Survival following cerebral infarction has improved over time. There has been a significant improvement in subarachnoid hemorrhage survival,[11] in part due to the diagnosis of less severe cases because of improved diagnosis with CT scanning and angiography. We are also better able to identify the etiology of subarachnoid hemorrhage cases, which is thought to influence outcome. Whether or not increased survival was related to better early treatment of patients with aneurysms was difficult to assess because of the small numbers of patients.

The 1-year overall survival of stroke is roughly the same for men and women and has improved over time. This improvement is thought to be due to a combination of factors including a reduction in stroke severity at onset associated with increased detection of small, less severe strokes and better care of stroke patients overall.

Survival at 5 years varies depending on whether the diagnosis is transient ischemic attack (TIA) or a stroke. The accuracy of diagnosis is a problem in the study of transient ischemic attack. It is never certain whether transient symptoms were ischemic or due to some other cause. But allowing for this uncertainty, survival at 5 years is significantly better for transient ischemic attack vs a definite ischemic stroke. For the population in Minnesota following an ischemic stroke, the expected 5-year survival of an age- and sex-matched control population is 78%.[10] This compares to 5-year survival of 66% for those diagnosed with transient ischemic attack, and 48% 5-year survival for those diagnosed with ischemic stroke.[10] With 5-year survival just a little under 50%, it is evident that stroke is a serious disease.

Risk of Recurrent Stroke

Individuals who have had a transient ischemic attack (TIA) or an ischemic stroke are at risk of a subsequent stroke. Following a transient ischemic attack, the risk of stroke occurrence at 1 month, 6 months, 1 year, and 5 years is 7.2%, 8.3%, 12.9% and 27.9%, respectively.[10] Following an ischemic stroke, the risk of stroke recurrence at 1 month, 1 year and 5 years is 2%, 5% and 32%, respectively.[10] At 5 years, the risk of stroke recurrence is about 30% following either TIA or stroke. At 1 month following a TIA, the risk for an incident stroke can be as high as 12%. An emergency department study of TIA patients found that 5% had a stroke within 48 hours of presentation.[12]

Given the high risk of stroke following a diagnosis of TIA, the manner in which individuals with TIA are evaluated in emergency departments throughout the world is frustrating to stroke physicians. There is the perception that something transient is benign.

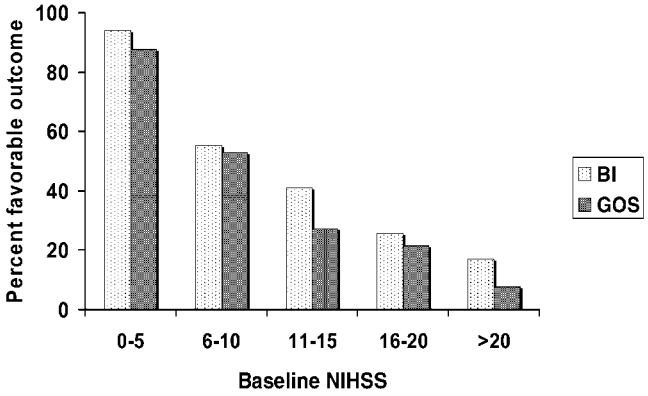

Figure 4. *Stroke outcome at 3 months related to baseline stroke severity (NIHSS) assessed by the Barthel index (BI) and the Glasgow outcome scale (GOS).*[13]

There is a significant risk of stroke if the diagnosis of TIA is accurate. As documented above, there is a high risk of stroke within the first few days after a TIA; and at 1 year, the risk for stroke following TIA is 12.9%. The overall incidence of recurrent stroke has been shown to be even higher in patients with underlying cardiac disease and cardiac source of embolism as the cause of stroke.[10]

Predictors of Stroke Outcome

The two strongest predictors of outcome for all stroke types are age and severity at stroke onset. Figure 4 shows data from the NINDS tissue plasminogen activator (t-PA) for acute ischemic stroke study demonstrating the effect of baseline stroke severity on outcome 3 months after stroke onset assessed by the Barthel index and the Glasgow outcome scale.[13] The percentage of patients with favorable outcome defined as being normal or near normal 3 months after stroke onset is measured on the Y-axis. Baseline stroke severity was assessed using the National Institute of Health Stroke Scale (NIHSS); scores 0–5 are mild stroke, while scores more than 20 are severe stroke. An example of a severe stroke is a patient with a right hemisphere stroke with a dense left hemiplegia, eyes deviated to the right, drowsiness, and neglect on the left side.

In the same study, the likelihood of having a favorable outcome decreased with increasing age, preexisting disability, and a history of diabetes.[13] Other negative predictors of stroke outcome at the time of stroke onset include a history of prior stroke, the level of consciousness, and the blood glucose level.[14] A high blood glucose level is associated with increased lactate production in ischemic brain tissue, which is associated with a larger final infarct volume.

STROKE PREVENTION

Stroke Risk Factors

What are stroke risk factors in the population? How can we modify incidence, prevalence and mortality? Stroke risk factors overlap with those that contribute to ischemic heart disease. These include the well-established cardiovascular risk factors of hypertension, diabetes and smoking. Underlying heart disease, atrial fibrillation, carotid stenosis, and the prior occurrence of a transient ischemic attack or stroke are risk factors for stroke, as well.

The relative risk (RR) for stroke for various risk factors has been estimated from a number of different studies.[15] The risk of stroke is increased 3–5 times with hypertension, and could be as high as 8 times higher, depending on the severity of the hypertension. With cardiac disease, especially atrial fibrillation, the risk of stroke occurrence is high. Diabetes, cigarette smoking and heavy alcohol use are each associated with about the same elevation of stroke risk (RR for each in the range 1.0–4.0).

For primary prevention of stroke, the strategy is primarily risk factor modification, including treating hypertension and smoking cessation, as well as appropriate management of patients with atrial fibrillation. The appropriate evaluation of transient ischemic patients to determine the underlying cause will help prevent death or stroke.

Modification of Stroke Risk Factors

As mentioned above, hypertension can increase the RR of stroke up to 8-fold. The treatment of hypertension, including isolated sys-

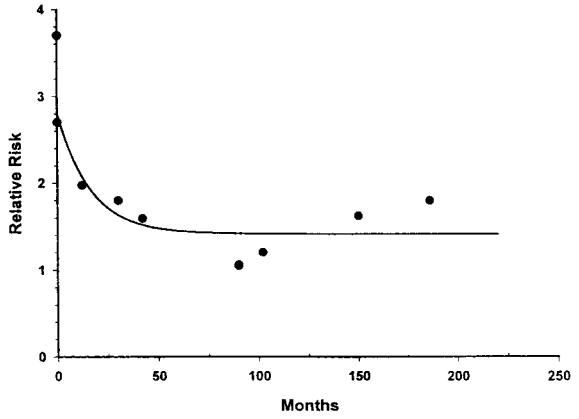

Figure 5. *Decline in relative risk for stroke after smoking cessation.[17] From: Lightwood et al, Short-term economic and health benefits of smoking cessation, myocardial infarction and stroke,* Circulation, *1997. Permission to republish granted by Lippincott Williams & Wilkins.*

tolic hypertension, has been shown in many clinical trials to reduce the risk of stroke at all levels of hypertension.[16] Recognizing and treating hypertension is the single most important thing that clinicians can do to reduce the risk of stroke in the population at large.

With cigarette smoking, there is an approximate 2- to 3-fold increase in stroke risk. Smoking accelerates atherosclerosis, and it also has effects on hemostasis that result in hypercoagulation. Smoking cessation does reduce the risk of stroke within 1–3 years of cessation.[17] Figure 5 illustrates the time course of stroke risk following smoking cessation, although the relative risk never gets back to 1. This is likely due to residual atherosclerosis in these individuals. The risk reduction in the first year is probably due to the reduction in the hypercoagulable effects of cigarette smoking.

Diabetes increases the risk of stroke, but unfortunately better management of diabetes has not been associated with a decrease in the risk of stroke. However, that doesn't reduce the importance of optimum diabetes management to realize the many benefits that result from good control.

Hyperlipidemia has a complex relationship with stroke and risk associations are not as clearly defined as in ischemic heart disease. In part, this is because stroke is more heterogeneous in cause than ischemic heart disease. Because there are other causes for stroke besides atherosclerosis, it has taken time to determine the effect of hyperlipidemia on stroke risk. Meta-analyses have shown that treatment of hyperlipidemia in patients with no history of stroke reduces the risk of stroke.[18]

With widespread HMG CoA reductase inhibitor (statin) drug use to lower lipids, separation of the effect of lipid lowering from the other actions of statins is difficult. However, the evidence suggests that lowering lipids reduces not only the risk of ischemic heart disease but also the risk of stroke, as well. The Heart Protection Study[19] involved heterogeneous groups of patients with vascular disease. With simvastatin therapy, there was a significant reduction (20%-25%) in stroke, MI, and mortality to a degree comparable to the effect of antiplatelet drugs. This effect was seen in patients with both elevated cholesterol and normal cholesterol levels. Effects of statin therapy other than lowering lipids are thought to contribute to the reduction of the vascular event rate.

Homocysteine is being evaluated as a stroke risk factor. Homocysteine has been linked to a slightly increased risk of ischemic heart disease and stroke in population studies.[20] Whether therapy to lower homocysteine levels will reduce the risk of stroke and ischemic heart disease is unknown.

Predictors of Recurrent Stroke

If an individual has already had a stroke, what is the conditional probability of recurrent stroke? For this population, the risk of recurrent stroke depends primarily on the underlying cause (ie, whether the stroke was due to large vessel disease, small vessel disease, carotid stenosis, or atrial fibrillation).

Non-valvular atrial fibrillation (AF) will be explored in some detail. The Stroke Prevention in Atrial Fibrillation (SPAF) studies I, II, and III looked at the prevention of stroke in patients with AF. SPAF III tried to identify those patients who would most benefit from the use of Coumadin, because it was thought

not every patient with AF requires Coumadin to prevent stroke.

Patients with one or more of the following characteristics were considered to be high risk: women over the age of 75 years, systolic hypertension, impaired left ventricular function, or previous systemic embolism. These high-risk patients were treated with warfarin (adjusted INR of 2–3) or low dose warfarin plus aspirin (1–2 mg warfarin plus aspirin 325 mg per day at fixed doses). Those patients considered as low risk were treated with aspirin 325 mg per day alone. The study had to be stopped because the high-risk patients receiving warfarin (adjusted by INR) had significantly fewer strokes than those receiving the low dose warfarin and aspirin regimen.[21] The latter treatment approach has been abandoned as a means of stroke prevention in patients with AF.

This study also found that impaired left ventricular function was not as powerful of a predictor for stroke risk as previously thought. Unadjusted annual stroke event rates for history of prior embolism were 11%, for systolic hypertension 12.4%, and for women over the age of 75 years 11.5%. In contrast, the unadjusted annual stroke event rate for persons with impaired LV function was 4.2%. With an average 5% annual risk of stroke for all non-valvular AF patients, the 10% or greater risk associated with these predictors of stroke in patients with non-valvular AF is significantly elevated. For the group treated with aspirin only, the event rate was a significantly lower 2.6% per year.[22] Stroke risk is even lower, about 0.05% per year, in AF patients under the age of 60 years without any underlying structural heart disease or hypertension.

Thus, based on underlying patient characteristics, there is a differential risk of stroke in patients with AF. Overall, warfarin is an effective drug for preventing stroke in AF patients; and in Figure 6, the results of the number of different trials are shown. The left bar shows the annual incidence of strokes in the placebo arm of each trial; the right bar shows the annual incidence of strokes in the warfarin arm of these trials. There is a significant and impressive risk reduction with warfarin across all of these studies. The question is whether warfarin should be given to every patient with AF. Based on the results of the SPAF studies, we can identify AF patients with a low risk for stroke (those not ''high risk'' per the study criteria mentioned above, especially those under age 60 without structural heart disease) who can be treated with aspirin.

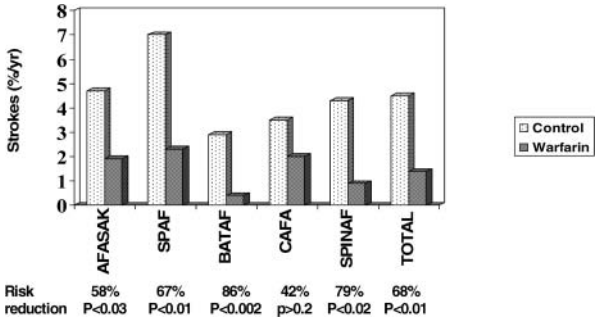

Figure 6. *Efficacy of warfarin for stroke prevention in non-valvular atrial fibrillation.*

Carotid Stenosis and Stroke

Carotid endarterectomy (CEA) significantly reduces the risk of recurrent stroke in patients with symptomatic carotid stenosis of more than 70%.[23] In patients with 50%-69% stenosis, the benefit of CEA is not as great, and CEA can be performed more selectively. Patients with hemispheric events with moderate carotid stenosis will benefit from CEA. With less than 50% carotid stenosis, there is no benefit obtained from CEA. Risk can be stratified based on the degree of carotid arterial stenosis to determine whether the patient's risk of stroke will be reduced with CEA.

Although clinical studies have shown that CEA reduces the risk of stroke in patients with asymptomatic carotid stenosis estimated at more than 60% by ultrasound, the absolute benefit in terms of stroke risk reduction is only 1.5% at 2 years.[23] There is still considerable debate as to whether CEA should be performed routinely in patients with asymptomatic carotid artery stenosis.

A commonly asked question is whether duplex scans of the carotids should be obtained routinely in patients who have stroke risk factors. None of the professional organizations representing stroke health professionals currently recommend performing screening carotid duplex studies in asymptomatic individuals. There are no good data that enable the selection of patient subgroups at highest risk of stroke that may benefit from being studied. Management of obvious risk factors such as elevated blood pressure should take precedence. One faces a management dilemma if the result shows the presence of severe, asymptomatic carotid stenosis.

Effects of Other Drugs on Stroke Prevention

There is universal agreement that antiplatelet drugs including aspirin, Aggrenox (dipyridamole and aspirin) and Plavix (clopidogrel) are effective in preventing vascular events.[24] However, current evidence indicates that while antiplatelet drugs are effective in preventing primary ischemic heart disease events, they are not effective in preventing primary stroke. For secondary stroke prevention, these drugs play a more important role reducing the risk of recurrent stroke by about 20%. While there is evidence that there is a differential effect between aspirin, Plavix and Aggrenox in reducing the risk of stroke, the differences are only moderate and aspirin is regarded as the most cost effective antiplatelet drug.[24]

There is a lot of debate as to whether ACE inhibitors have clinically significant vascular event preventing effects beyond simply lowering blood pressure. The HOPE[25] and PROGRESS[26] studies evaluated the use of ACE inhibitors on vascular event prevention. The HOPE study included a heterogeneous group of patients with different vascular diseases and showed a 22% risk reduction in the composite endpoint of MI, stroke and vascular death in patients at high risk of vascular disease treated with ramipril. The PROGRESS study involved the use of perindopril with or without indapamide to prevent recurrent stroke in patients who had either a cerebral infarct or an intracerebral hemorrhage. There was a 28% relative risk reduction in recurrent stroke in this study. Currently, most stroke physicians would favor the use of an ACE inhibitor in patients who have already had a stroke. However, as noted above, there is debate as to whether the vascular event prevention benefit associated with the use of the drug is an anti-hypertension effect or a class effect of the drug.

IMPROVING STROKE OUTCOMES

There are other new advances in stroke care that do not simply involve the use of drug therapies. Instead, these advances involve the reorganization of stroke care services with the goal of providing better stroke care to the whole population.

Treatment of acute ischemic stroke patients with t-PA within 3 hours of stroke onset is associated with improved patient outcomes. This finding was reported in 1995[27] and was followed by FDA approval of t-PA to treat acute ischemic stroke patients within 3 hours of stroke onset in 1996. The t-PA study[27] demonstrated that if t-PA is given according to the study protocol, there is a 30% increase in the likelihood of having a normal or near normal outcome, even though there is a higher incidence of symptomatic intracerebral hemorrhage (6.5%) in the t-PA treated group. Mortality was not different between the placebo and treatment groups. At present, this is the only intervention available to improve the outcome of acute stroke and requires having a system in place to assess and treat patients within 3 hours of stroke onset. Since diagnostic evaluations and consideration of treatment options take at least 1 hour, acute stroke patients have to arrive in the emergency department within 2 hours of the onset of stroke symptoms.

However, fewer acute ischemic stroke patients than expected have been treated with t-PA because of concerns about the safety and efficacy of this therapy for acute ischemic stroke.[29] Some studies have shown a high in-

cidence of adverse outcomes when treating acute ischemic stroke patients with t-PA, but this has been attributed primarily to lack of adherence with the treatment protocol.[29] Good outcomes following the use of t-PA to treat acute ischemic stroke have been reported in experienced institutions that adhere to the study treatment protocol.[29]

These observations have lead to international discussions about the need to identify the resources that are needed to rapidly evaluate and treat acute stroke patients. Primary stroke center criteria have been proposed that will identify institutions that are capable of providing appropriate acute stroke care.[30] These centers are capable of the following things: rapidly distinguishing between ischemic stroke and intracerebral hemorrhage; identifying and treating other medical problems such as arrhythmias, hypertension, fever and significant deviations in blood glucose; and giving t-PA to appropriately selected patients.

Stroke units are an important component of primary stroke centers. Stroke units have been shown to reduce both stroke morbidity and mortality by approximately 20%.[31] Prevention of aspiration, prevention of deep vein thrombosis and pulmonary embolism, early rehabilitation, and implementation of appropriate secondary prevention medication are responsible for this result. Primary stroke centers also reduce the number of survivors who depend on others for support either at home or in a health care facility. Based on available evidence, organized care in primary stroke centers that have stroke units should lead to a significant improvement in acute stroke morbidity and mortality.

Based on a presentation to the American Academy of Insurance Medicine in Scottsdale, Ariz, October 14, 2003.

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