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REVIEW

Preventing recurrent cerebrovascular events in patients with stroke or transient ischemic attack: The current data

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Abstract

Purpose: To describe recurrent stroke in relation to the current data, treatment guidelines, diagnostic considerations, risk prevention, and management for the nurse practitioner (NP).
Data sources: An extensive review of the scientific literature, clinical trials, and clinical guidelines.
Conclusions: Recurrent stroke is a major health concern. A first ischemic cerebrovascular event or transient ischemic attack (TIA) is a risk factor for future strokes.
Implications for practice: The risk of recurring stroke has been demonstrated in multiple studies, yet only approximately 5% of stroke patients receive appropriate therapy in a timely manner. The stroke or TIA workup should be completed quickly so that the appropriate treatments and interventions can be initiated to reduce the risk of an additional event. The etiology of the stroke and identification of personal risk factors are important because treatment depends on the specific stroke mechanism. A variety of antiplatelet trials have specific implications for stroke and recurrent stroke. Present treatments include aspirin, aspirin plus extended-release dipyridamole and clopidogrel. The NP plays an important role in ongoing patient education about symptoms, the long-term management of the patient, and reduction of future stroke risk.

According to the National Center for Health Statistics mortality data, stroke remains a major public health concern. Annually, nearly 900,000 patients are discharged from hospitals with a diagnosis of stroke. When considered separately from other cardiovascular diseases, stroke ranks third among all causes of death, behind heart disease and cancer (Lloyd-Jones et al., 2010). Stroke continues to be a leading cause of long-term disability in the United States (Centers for Disease Control and Prevention, 2001a,b), with projected direct and indirect costs of more than $2 trillion between 2005 and 2050 (Lloyd-Jones et al., 2010).

Modern stroke care poses unique challenges to the nurse practitioner (NP) in diagnosis, care, risk prevention, patient education, and follow-up. The latest guidelines state that it is imperative to complete a comprehensive and timely evidence-based workup in patients with stroke or transient ischemic attack (TIA) to reduce morbidity and mortality and to initiate appropriate treatments (Adams et al., 2007). In addition to recommending

lifestyle changes to a patient, it is also important to treat comorbid diseases, such as hypertension, dyslipidemia, and diabetes. Consequently, the role of the NP in the treatment of modifiable risk factors and patient follow-up is critical to improved outcomes. While the NP may not always diagnose and create the treatment plan for these patients, an understanding of the mechanism and pathophysiology of ischemic and nonischemic stroke is necessary to carry through an individual treatment plan with each patient that is specific to his or her needs. NPs must be aware of their unique role at several stages of treatment for patients with a history of stroke and TIA.

Cerebrovascular events

Cerebrovascular events occur as a result of an obstruction of the blood supply to an area of the brain, or to the blood supply that surrounds the brain. There are several types of cerebrovascular events. Ischemic stroke is generally classified as having an embolic or thrombotic origin, whereas hemorrhagic stroke involves bleeding within the brain. Patient histories, including headache or recent head injury, are important in the diagnosis of this condition. The definition of TIA has recently been revised to "a brief episode of neurological dysfunction caused by a focal disturbance of brain or retinal ischemia, with clinical symptoms typically lasting less than 1 h and without evidence of infarction" (Albers et al., 2002). TIA is being viewed more seriously and is considered a medical emergency as a result of its correlation with increased risk of recurrent stroke.

Close to 25% of the 795,000 strokes that occur annually in the United States are recurrent in nature, meaning that they have been preceded by a previous cerebrovascular event, such as another stroke or TIA (Lloyd-Jones et al., 2010). Specifically, there is an average risk of a recurrent stroke of about 30%–40% at 5 years past the first cerebral infarction (Petty et al., 1998; Sacco et al., 2006). Likewise, studies have shown that 15% of all stroke cases are preceded by a TIA (Hankey, 2003). Even so, many patients who experience a TIA never report it to their healthcare provider (Johnston et al., 2003). The risk of stroke is much higher in the first few days after a TIA, with studies indicating an approximately 3%–6% 2-day risk of stroke after a TIA, with about 45%–65% of strokes occurring in the first 30 days (Hill et al., 2004; Kleindorfer et al., 2005).

A prospective study, EXPRESS, in the United Kingdom, and an observational study, SOS-TIA, in France, evaluated the effect of rapidly assessing and treating TIA or minor ischemic stroke. EXPRESS studied the effect of reducing assessment and treatment times to 1 day, from their standard of care of 3 days for assessment and 20 days to first prescribed treatment. The SOS-TIA study analyzed the effects of rapid assessment (within 4 h of presentation) of patients who presented to a hospital-based clinic with 24-h access and displayed symptoms suggesting TIA. Both studies saw an 80% reduction in 90-day stroke risk and demonstrate exactly how important the NP's role in rapid and accurate assessment and immediate treatment can be for the patient (Lavallee et al., 2007; Luengo-Fernandez et al., 2009).

Acute evaluation

The NP has a unique role in all stages of stroke treatment, beginning with the initial stroke evaluation, diagnosis, treatment, and, finally, patient education. It is this initial evaluation that is important to stabilize the patient, to assess his or her particular neurological deficits, and to diagnose an ischemic stroke as soon as possible. Moreover, a timely evaluation is critical as a result of the narrow 3-h therapeutic window in which one can use intravenous thrombolytics (Adams et al., 2007; Barber et al., 2001). Although the American Stroke Association/American Heart Association (ASA/AHA) has recently expanded the therapeutic window from 3 to 4.5 h for treatment with thrombolytics in eligible patients, the benefits of later therapy are not clear and time is still of the essence (Del Zoppo, Saver, Jauch, & Adams, 2009). Time from symptom onset is the single most important piece of information in the initial assessment. In addition, early assessment is particularly important because stroke or TIA symptoms may look similar to those of other conditions, such as hypoglycemia, migraine, seizure, trauma, or medication overdose.

Stroke workup and diagnostic testing. The AHA overview on nursing for ischemic stroke patients states that the initial phase of treatment should focus on identifying stroke symptoms, the nature and location of the infarct, eliminating stroke mimics, and assessing the patient for risk of acute and long-term complications before determining treatment (Summers et al., 2009). The NP should be trained to administer a stroke scale, such as the National Institutes of Health Stroke Scale, which is rapidly becoming the standard by which neurological function is measured, to determine not only the severity of the stroke, but the effectiveness of treatment. In addition, neurological assessment should include vital signs, cardiac monitoring, and a baseline neurological assessment (Summers et al., 2009).

A stroke workup and diagnostic testing are necessary to determine the etiology of the stroke. The pathophysiology of ischemic stroke and TIA include, but are not limited to, atherosclerotic plaque buildup,

thrombosis, and embolism. The initial stroke workup should aid in differentiating if the stroke is ischemic or hemorrhagic in nature. A noncontrast computed tomography (CT) of the head is usually performed (Adams et al., 2008). Further imaging with magnetic resonance imaging (MRI) and magnetic resonance angiography or CT of the head and neck should be obtained to assess the brain and blood vessels of the head and neck (Adams et al., 2008). In addition, a transthoracic echocardiogram/transesophageal echocardiogram and/or cardiac MRI can be conducted to diagnose thrombosis, patent foramen ovale, and/or endocarditis (Adams et al., 2008). Because there is a high incidence of cardiac disease in stroke patients, cardiac monitoring for irregular rhythms is useful, including a screen for acute cardiac arrhythmia and atrial fibrillation (AF) (Adams et al., 2008). Although obtaining a chest x-ray has previously been recommended, this is no longer the case (Adams et al., 2007).

A workup for hypercoagulable states is recommended as well as blood testing for hemostasis (Christensen, Fogh Christensen, & Boysen, 2005; Sacco et al., 2006). In the acute stroke/TIA workup, the NP should obtain a complete blood count to ascertain platelet levels for clotting, international normalized ratio (INR) to measure clotting time, a comprehensive metabolic panel, fasting lipid panel to measure the risk for developing cardiovascular disease, hemoglobin A1C, and serum cardiac enzymes, and should perform a 12-lead electrocardiogram. Blood glucose testing can diagnose hypoglycemia, a common stroke mimic.

TIA is handled somewhat similarly to stroke, and current class I evidence suggests the use of neuroimaging within 24 h of symptom onset, diffusion-weighted MRI and CT if MRI is not available (Easton et al., 2009). In addition, noninvasive imaging of cervicocephalic vessels should be performed routinely as part of a TIA evaluation, as well as noninvasive testing to exclude the presence of intracranial vascular stenosis (Easton et al., 2009).

Modifiable and nonmodifiable risk factors

Although cardioembolic stroke accounts for approximately 25% of ischemic strokes, other cerebrovascular events may present to the NP, such as large-vessel atherosclerosis, small-vessel occlusive disease (which leads to lacunar stroke), and other rare and often unknown conditions that may account for a patient's symptoms. The identification of risk factors is important for the diagnosis of these conditions as well as for the future management of the patient. Nonmodifiable risk factors include age, gender, race, and ethnicity, as well as family history and medical history. Indeed, patients with a history of stroke or TIA are at a higher risk of stroke than individuals without such a history (Hill et al., 2004; Kleindorfer et al., 2005).

In addition to these nonmodifiable risk factors, there are many modifiable risk factors that can help to improve the health of patients and offer the NP an opportunity to educate patients. The AHA/ASA guidelines indicate that TIA has the same basis for secondary prevention as stroke itself (Sacco et al., 2006). The identification and management of modifiable risk factors reduces both the incidence of recurrent stroke and TIA. Modifiable risk factors include management of hypertension, treatment of dyslipidemias, diabetes, smoking cessation, moderation of alcohol use, increase in physical activity, weight loss, and reduced sodium intake (Chobanian et al., 2003).

Dyslipidemia is treated with a goal of reducing low-density lipoprotein (LDL) cholesterol. Statins are considered to be the gold standard for treating high LDL cholesterol levels (Amarenco et al., 2006), and high-dose atorvastatin has been shown to reduce the risk of stroke and other cardiovascular events in patients who have had a previous stroke or TIA, despite a small increase in the incidence of hemorrhagic stroke (Johnston et al., 2006). Nonetheless, lifestyle changes, such as weight loss and healthy eating, are important additional means that can be initiated by the NP to reduce this risk factor (Grundy et al., 2004).

Diabetic patients should be treated aggressively to reduce the likelihood of a second stroke. As in dyslipidemia, lifestyle changes, such as weight loss, can be effective in moderating the risk of diabetes (American Diabetes Association, 2010). In addition, adults with diabetes should be treated with a statin to lower the risk of a first stroke. Treatment with an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) as well as tight control of hemoglobin A1C and fasting blood glucose levels should be considered to help achieve a goal blood pressure of less than 130/80 mmHg and to reduce the progression of renal disease (American Diabetes Association, 2010).

Hypertension may be treated with a variety of therapies. Thiazide diuretics are recommended for most patients with uncomplicated hypertension. However, most people with hypertension will require two or more hypertensive agents, including thiazide diuretics, ACEIs, ARBs, β-adrenergic receptor blockers, and calcium channel blockers (Chobanian et al., 2003). These reduce cardiovascular risk, including the risk of stroke, in patients with hypertension (ALLHAT Officers, 2002; Neal, MacMahon, & Chapman, 2000; Turnbull, 2003). Management of blood pressure is essential because the relationship between blood pressure and cardiovascular disease is continuous, consistent, and independent of

other risk factors (Chobanian et al., 2003). The risk of cardiovascular disease such as stroke doubles with every increment of 20/10 mmHg over 115/75 mmHg (Chobanian et al., 2003).

Pharmacological management of cardioembolic stroke

Anticoagulant therapy, such as warfarin, is recommended to prevent cardioembolic stroke in patients with AF (Albers, Amarenco, Easton, Sacco, & Teal, 2008; Sacco et al., 2006; Sacco, Sivenius, & Diener, 2005). Ischemic stroke tends to occur in AF patients as a result of the formation of thrombus in the left atrium. Subsequently, the resulting emboli migrate to the cerebrovascular system (Lloyd-Jones et al., 2010). The European Atrial Fibrillation Trial demonstrated the superior efficacy of anticoagulation over aspirin in recurrent stroke patients with a previous TIA (Connolly et al., 2006; EAFT Study Group, 1993). In the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events study, anticoagulation therapy was found to be superior to the combination of clopidogrel and aspirin (clopidogrel 75 mg/day, aspirin 75–100 mg/day; $n = 3335$) for the prevention of AF-associated stroke (Connolly et al., 2006). The ACTIVE A/ACTIVE W Trials demonstrated that treatment with clopidogrel plus aspirin compared with aspirin alone did reduce the rate of major vascular events among the patients with AF who were at increased risk for stroke and who could not tolerate warfarin; however, there was a significant increase in major hemorrhage (Connolly et al., 2006). For those patients who are unable to tolerate oral anticoagulants, aspirin alone is recommended (EAFT Study Group, 1993; Stroke Prevention in Atrial Fibrillation Investigators, 1996).

Pharmacological management of noncardioembolic stroke. Antiplatelet therapy has emerged as a fundamental treatment for noncardioembolic recurrent stroke reduction. Antiplatelet therapy is used in acute cerebrovascular ischemia for several reasons. It is used to prevent recurrent thrombosis, to halt thrombus propagation in partially occluded vessels, to prevent embolization, and to prevent other complications related to stroke, such as deep vein thrombosis, pulmonary emboli, and myocardial infarction (MI) (Antithrombtic Trialists' Collaboration, 2002; Sacco et al., 2006). The treatment question facing the NP is not whether to use antiplatelet therapy, but which antiplatelet therapy is best suited to the patient. Presently, there are three commonly used and recommended antiplatelet treatments: aspirin, clopidogrel, and aspirin plus extended-release dipyridamole (ER-DP).

Aspirin. Aspirin inhibits platelet aggregation through irreversible inhibition of cyclooxygenase (Roth & Majerus, 1975). As aspirin was the first antiplatelet inhibitor, it is frequently the standard against which all other antiplatelet therapies are compared (Adams et al., 2007). Early trials with aspirin demonstrated it to be effective in preventing serious vascular events. A cumulative meta-analysis of 11 clinical trials of 10,000 patients with previous cerebral ischemia indicated that it reduces the relative risk of stroke by 13% (Algra & van Gijn, 1999). In addition to effects on primary stroke, aspirin at doses of 50–1300 mg/day has been shown to reduce recurrent stroke or TIA (Adams et al., 2008; Antithrombotic Trialists' Collaboration, 2002; Sacco et al., 2006) with at least one study showing efficacy at doses as low as 30 mg/day (Dutch TIA Trial Study Group, 1991). Indeed, it seems that lower doses of aspirin have similar clinical efficacy in preventing stroke, with a dose-dependent decreased risk of bleeding over higher doses (Antithrombotic Trialists' Collaboration, 2002).

Clopidogrel. Clopidogrel acts by irreversibly modifying the P2Y12 adenosine diphosphate (ADP) receptor, thus inhibiting ADP-dependent platelet aggregation. It is a prodrug that undergoes extensive hepatic metabolism; clopidogrel takes between 3 and 7 days to maximally inhibit platelet aggregation at a 75-mg dose (Clopidogrel prescribing information, 2009), as evaluated by optical aggregometry (Gorchakova et al., 2004). The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study was the first study comparing clopidogrel with aspirin and looked at a combined measure of MI, stroke, and vascular death in patients with stroke, MI, or peripheral arterial disease. The clopidogrel group had a 5.32% annual risk of the combined measure (vs. 5.83% for aspirin; relative risk reduction [RRR] = 8.7%), which barely reached statistical significance ($p = .043$). The achievement of this composite endpoint appears to have been driven largely by efficacy in peripheral arterial disease patients. Interestingly, patients in CAPRIE who had had a first ischemic stroke were seven times as likely to have a second stroke than to have an MI, lending support to the now well-established argument that after a stroke, a patient is more likely to have another stroke than an MI as the next vascular event (CAPRIE Steering Committee, 1996).

Because clopidogrel's mechanism of action differs from that of aspirin, the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance and Management of Atherothrombosis with Clopidogrel in High-risk patients with recent TIA or ischemic stroke trials were conducted to see if clopidogrel plus aspirin had any specific advantage over monotherapy (Diener et al., 2004). Significantly, these

trials demonstrated an increase in life-threatening bleeding and intracerebral hemorrhage with clopidogrel plus aspirin (Bhatt et al., 2006, 2007). Guidelines specifically recommend against using clopidogrel plus aspirin in stroke or TIA patients (Adams et al., 2007, 2008).

Dipyridamole. Dipyridamole plus aspirin has emerged as a new therapy for cardiovascular disease; there has been great interest in its effect in ischemic stroke and recurrent stroke. Dipyridamole exerts antiplatelet effects through the vessel wall (Eisert, 2001) and has antioxidant (Iuliano et al., 1995) and anti-inflammatory (Weyrich et al., 2005) properties.

As with aspirin, dipyridamole has been shown to have an effect on recurrent stroke prevention. Specifically, the combination of ER-DP plus aspirin has been shown to reduce recurrent ischemic stroke and is superior to aspirin alone (Diener et al., 1996; Wilterdink & Easton, 1999). In addition, the benefit in efficacy increases in higher-risk patients (Albers et al., 2008; Leonardi-Bee et al., 2005). The European Stroke Prevention Study 2 (ESPS-2) demonstrated that aspirin plus ER-DP prevented almost twice as many recurrent strokes as aspirin alone (Diener et al., 1996).

Both ESPS-2 and the European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) demonstrated that dual therapy of dipyridamole plus aspirin is substantially more effective than aspirin alone. ESPS-2, a large study with more than 6000 patients, examined the effectiveness of dipyridamole plus aspirin in reducing recurrent ischemic stroke after a first event. Specifically, relative stroke risk over 2 years was reduced 18% with aspirin alone and 37% by ER-DP in combination with aspirin compared with placebo. Moreover, the 2-year rate of recurrent stroke in ESPS-2 was 9.5% for ER-DP plus aspirin compared with 12.5% for aspirin alone and 15.2% for placebo (Diener et al., 1996; Halkes et al., 2006).

The ESPRIT trial, in which immediate-release dipyridamole was used, expanded on these results as patients were given between 30 and 325 mg/day of aspirin so as to more accurately reflect clinical experience. The median dosage of aspirin was 75 mg, and prescribed doses of aspirin was similar across both groups. In addition, whereas the primary endpoint of ESPS-2 was stroke, ESPRIT had a combined endpoint of vascular death, nonfatal stroke, nonfatal MI, and bleeding complications. The ESPRIT researchers found that with dipyridamole plus aspirin there was a 13% risk of reaching this endpoint, while with aspirin alone there was an increased risk of 16%. Taken together this resulted in an RRR of 20% for dipyridamole plus aspirin (Halkes et al., 2006).

A meta-analysis of 338,991 patients across 50 randomized, controlled trials compared antiplatelet agents including aspirin, dipyridamole, thienopyridines (clopidogrel and ticlopidine), and GP IIb/IIIa inhibitors, alone or in combination. The analysis showed that dipyridamole plus aspirin had the lowest rates of bleeding—even lower than aspirin alone (Serebruany, Malinin, Eisert, & Sane, 2004).

The PRoFESS trial. The Prevention Regimen For Effectively avoiding Second Strokes (PRoFESS) trial was the first head-to-head trial comparing aspirin plus ER-DP versus clopidogrel monotherapy; this trial involved 20,332 stroke patients worldwide. The primary endpoint was first recurrent stroke of any type. The secondary endpoint was the composite of stroke, MI, and vascular death. The trial failed to demonstrate noninferiority, although it also did not demonstrate superiority for either regimen. The primary endpoint event rate was similar for both aspirin plus ER-DP and clopidogrel (11.7% vs. 11.4%; hazard ratio: 1.03; 95% confidence interval: 0.95–1.11). The secondary endpoint, a composite measure of stroke, MI, and vascular death, was identical in both groups (13.1%). Other endpoints, including death and MI, likewise showed no statistical difference between groups, with the exception of new or worsening heart failure, which was significantly less frequent in the ER-DP plus aspirin group (1.4% vs. 1.8%) The ER-DP plus aspirin arm had an increase in major hemorrhagic events compared with clopidogrel, including a higher number of hemorrhagic strokes (0.8% compared with 0.4%) but a lower number of recurrences of ischemic stroke (7.7% vs. 7.9%). The ER-DP plus aspirin group also had significantly fewer cases of new heart failure and less progression of chronic heart failure than the clopidogrel group (Sacco et al., 2008).

The purpose of a head-to-head study is to determine a clearly superior treatment choice in order to provide healthcare professionals guidance in therapy. The results from PRoFESS are unlikely to translate into meaningful changes in clinical practice or to end the debate of what is a preferable treatment for recurrent stroke. A lower-than-expected event rate, short follow-up time utilized in the study, and differing adherence to therapy in the groups may have reduced power in the study.

Patient education

NPs also serve a role in identifying modifiable risk factors in patients and educating these patients about the importance of these risk factors. In addition, in the case of a TIA or stroke event, patient education by an NP is particularly critical. Approximately 5 million Americans reported having had TIA symptoms, yet did not seek medical advice (Johnston et al., 2003). There is a general lack of education about the symptoms of a TIA or even the

fact that they are transient in nature. As a result, patients are likely to ignore a TIA. Patients must be made aware of stroke and TIA symptoms, and of the fact that a previous stroke or TIA predisposes them to a greater chance of having a stroke in the very near future. The nature of emergency interventions means that time to treatment after the onset of symptoms is critical. Delays in seeking medical attention make it difficult to get an accurate medical history or to document objective findings related to the symptoms as they are happening. A significant source of delays includes the patient consulting with his or her primary care physician or relatives at the onset of symptoms. Patients must be educated to call 911 for immediate transportation to a hospital instead (Agyeman et al., 2006; Lloyd-Jones et al., 2010).

Transition to outpatient care. The NP should know the etiology of a patient's particular stroke, as well as any prior treatments or interventions that took place during the patient's acute care. Once the diagnostic workup is complete and risk factors have been identified, the NP can use this information to individualize the treatment plan. It is important for the NP to make the patient understand the treatment plan because this will support patient compliance. The NP has an opportunity to educate the patient about the need for ongoing treatment and monitoring for the prevention of recurrent stroke during this transitional phase. In addition, a discussion can begin about the importance of the patient taking an active role in his or her health and recovery. Regular follow-up is needed to monitor a patient's modifiable risk factors and hopefully see that these risk factors are reduced over time. It is important for the NP to maintain regular contact with the patient. This assists in reinforcing ongoing patient education, maintaining the patient's adherence to therapy, and, if there are problems with adherence, modifying that patient's treatment according to his or her specific needs and circumstances.

Conclusions

Patient education by the NP is critical in preventing recurrent stroke. Patients who experience their first TIA or stroke are at increased risk for a second TIA or stroke and must be made aware of that fact. Specifically, prevention after a warning sign, such as a TIA, is more effective than intervention or therapy after a second attack. However, when patients do seek medical therapy, there is strong evidence that the use of antiplatelet therapy in patients with noncardioembolic stroke can reduce the risk of a recurrent attack. For patients with AF, anticoagulant therapy, such as warfarin, is recommended to prevent cardioembolic stroke if they can tolerate that drug. For those that cannot, clopidogrel plus aspirin or aspirin alone are recommended. Regardless of whether the patient has been admitted for a TIA or stroke, a thorough history, physical assessment, identification of risk factors, and complete diagnostic workup are critical to determining subsequent treatment decisions. The NP must determine whether these ongoing treatments are appropriate for the patient based on his or her lifestyle and risk factors and must also establish and maintain patient compliance through education and support. In addition to developing an appropriate treatment plan based on the type of stroke the patient had and the risk factors identified, the NP will also need to consider the patient's resources to increase compliance with a treatment plan and reduce the risk of a recurrent stroke.

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