The last year has seen advances in both primary and secondary prevention of stroke, including significant steps forward in our understanding of the risks and benefits of anticoagulation in nonvalvular atrial fibrillation (AF) and in assessment of the benefits of urgent treatment after transient ischemic attack (TIA) and minor stroke.

Nonvalvular AF affects about 1% of the population with its prevalence increasing sharply with age. AF is associated with a 5-fold increase in stroke risk. Although warfarin is effective in the secondary prevention of ischemic stroke in the majority of patients with nonvalvular AF, uncertainties remain about the optimal use of warfarin in routine clinical practice in the primary prevention setting. Research published in 2007 helps to resolve several outstanding questions.

A systematic review analyzed the efficacy and safety of antiplate-thrombotic agents in the primary prevention of stroke in patients with nonvalvular AF. This review added 13 recent randomized trials to a previous meta-analysis of all published trials with a mean follow-up of 3 months or longer. Compared with the control, adjusted-dose warfarin (6 trials, 2900 participants) reduced stroke by 64% (95% CI, 49 to 74), whereas antiplatelet agents (8 trials, 4876 participants) reduced risk by 22% (95% CI, 6 to 35). Adjusted-dose warfarin was substantially more efficacious than antiplatelet therapy (12 trials, 12963 participants; relative risk reduction 39%; 95% CI, 22 to 52). Absolute increases in major extracranial hemorrhages were small (≤0.3% per year). Thus, warfarin was substantially more efficacious than antiplatelet therapy.

Because the absolute risk of stroke varies widely among patients with nonvalvular AF, the overall results of trials and meta-analyses of antithrombotic treatment cannot necessarily be generalized to all individuals. To balance the benefits and risks of chronic antithrombotic prophylaxis, it is important to estimate the absolute risk of stroke for individual patients. Another recent systematic review addressed this question and evaluated all studies that had used multivariate regression techniques to identify independent risk factors for stroke in patients with nonvalvular AF. Among 7 studies (including 6 entirely independent cohorts), prior stroke or TIA (relative risk [RR] 2.5; 95% CI, 1.8 to 3.5), increasing age (RR 1.5 per decade; 95% CI, 1.3 to 1.7), a history of hypertension (RR 2.0; 95% CI, 1.6 to 2.5), and diabetes mellitus (RR 1.7; 95% CI, 1.4 to 2.0) were the strongest, most consistent independent predictors of stroke. Observed absolute stroke rates for nonanticoagulated patients with single independent risk factors were in the range of 6% to 9% per year for prior stroke/TIA, 1.5% to 3% per year for history of hypertension, 1.5% to 3% per year for age >75 years, and 2.0 to 3.5% per year for diabetes. Female sex was inconsistently associated with stroke risk. Evidence that either heart failure or coronary artery disease were independently predictive of stroke was inconclusive.

Persons age >75 years account for more than half of all cases of stroke related to AF and the prevalence of AF is about 12% in this age group. Several studies have shown that the risk of serious anticoagulation-associated hemorrhage rises with age. Because the elderly are under-represented in most of the randomized trials, particularly those conducted in a primary care setting, concern has long been expressed regarding the applicability of trial evidence to older patients. Reinforcing this concern, another study published in 2007 highlighted the dramatic increase in incidence of anticoagulant-associated intracerebral hemorrhage in the elderly population in recent years. Joint American and European guidelines recommend anticoagulation in the presence of 2 or more risk factors for stroke in the setting of atrial fibrillation (one of which is age ≥75), but suggest that patients in this age group who are at increased risk of bleeding can be treated with a lower international normalized ratio target than was used in the randomized trials.

Two trials published in 2007 have provided much needed data on the safety and efficacy of warfarin versus aspirin in elderly patients. The first was a small open label study in ambulatory, cognitively intact patients aged 80 to 89 years with nonvalvular AF who were randomized to receive dose-adjusted warfarin (international normalized ratio 2.0 to 3.0) or aspirin 300 mg. During 1 year of follow-up in 75 patients (aspirin 39; warfarin 36, mean age 83.9 years), dose-adjusted warfarin was significantly better tolerated with fewer adverse events (mainly bleeding) than aspirin (13 versus 2, P=0.002). The second, much larger trial (Birmingham Atrial Fibrillation Treatment of the Aged study, BAFTA) was a prospective, randomized open-label trial with blinded evaluation of end points (PROBE design) in patients aged 75 years or over with nonvalvular AF treated in a primary care setting. The trial included 973 patients (mean age 81.5 years) assigned to...
warfarin (target international normalized ratio 2 to 3) or aspirin (75 mg per day). During a mean follow-up of 2.7 years, there were 24 primary events (21 strokes, 2 other intracranial hemorrhages, and 1 systemic embolus) in subjects assigned to warfarin and 48 primary events (44 strokes, 1 other intracranial hemorrhage, and 3 systemic emboli) in subjects assigned to aspirin (annual risk 1.8% versus 3.8%; RR 0.48; 95% CI, 0.28 to 0.80; P=0.003). The annual risk of extracranial hemorrhage was 1.4% for warfarin versus 1.6% for aspirin-treated subjects. Thus, the results of each of these trials support the use of anticoagulation therapy for people aged over 75 who have nonvalvular AF and no contraindications to treatment.

The advent and widespread use of modern neuroimaging technologies is leading to a reconsideration of the traditional definition of TIA as a high proportion of patients experiencing transient focal neurological symptoms from presumed ischemia have actually had permanent tissue injury. TIA patients are often managed nonemergently. An observational study conducted several years ago found that one-third of patients with a first-ever physician diagnosed TIA were not admitted to hospital.21 The study used a before-after design with independent, blinded audit of all strokes occurring within 90 days. Although there was no significant difference in stroke risk of TIA patients treated in-hospital between the 2 periods, the 90-day stroke risk in patients referred to the study clinic fell from 10.3% to 2.1% (adjusted hazard ratio 0.20; 95% CI, 0.08 to 0.49; P=0.0001) with more rapid assessment and treatment. A second study evaluated the impact of a hospital-based TIA evaluation clinic with 24-hour access.22 The observed 90-day stroke rate was 1.24% (95% CI, 0.72 to 2.12), whereas the rate predicted from ABCD² scores was 5.96%. Although not prospective randomized trials, these 2 studies support the urgent evaluation of TIA patients.

It is known that patients with TIA or minor nondisabling stroke related to a high-grade ipsilateral carotid stenosis benefit from early carotid endarterectomy.23 There are only limited data comparing the effects of specific medical interventions begun soon after TIA. In a factorial design, the Fast Assessment of Stroke and TIA to prevent Early Recurrence (FASTER) trial was designed to evaluate the effects of clopidogrel plus aspirin versus aspirin and simvastatin versus placebo begun within 24 hours of TIA or minor stroke. The trial was stopped early because of increased use of statins in the potential study population before TIA and slow recruitment. There was a nonsignificant reduction in the 90-day risk of stroke with clopidogrel+aspirin (risk ratio 0.7; 95% CI, 0 to 1.2) and a nonsignificant increase in stroke risk in those given simvastatin (risk ratio 1.3; 95% CI, 0.7 to 2.4) with no interaction between the 2 interventions (P=0.64). The results of FASTER are inconclusive and additional larger studies comparing urgent interventions for patients with TIA are needed.

Disclosures

None.

References


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