Primary Findings From Selected Recent National Institute of Neurological Disorders and Stroke-Sponsored Clinical Trials That Have shaped Modern Stroke Prevention

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NORTH AMERICAN SYMPTOMATIC CAROTID ENDARTERECTOMY TRIAL

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) answered practical questions relating to the efficacy and safety of carotid endarterectomy based on degree of carotid stenosis and accompanying medical comorbidity in patients with symptomatic carotid stenosis (The Canadian Cooperative Study Group, 1998; North American Symptomatic Carotid Endarterectomy Trial Collaborators, 1991). In summary, key findings were that carotid endarterectomy resulted in benefits for the following three outcomes among persons with 70% to 99% symptomatic carotid stenosis when compared with medical management alone: (1) ipsilateral stroke, (2) major or fatal ipsilateral stroke, or (3) stroke or death. However, the surgical risks outweighed any benefits among those with less than 50% symptomatic carotid stenosis. For those with severe carotid stenosis (70% or greater), the surgical treatment group experienced durable benefit at 8 years. For those with 50% to 69% symptomatic carotid stenosis, the benefits were more modest but, again, in favor of surgical treatment. Patients in the 50% to 69% treatment group with hemispheral cerebrovascular symptoms and those who were men had greater benefit from surgery than those who had retinal ischemic symptoms or who were women. Medical and surgical complications in NASCET were reviewed previously (Ferguson et al, 1999; Paciaroni et al, 1999).

REFERENCES


ASYMPTOMATIC CAROTID ATHEROSCLEROSIS STUDY

The Asymptomatic Carotid Atherosclerosis Study (ACAS) examined patients with asymptomatic carotid stenosis (60% or greater) and showed a modest benefit favoring carotid endarterectomy over medical management for reduction of ipsilateral stroke and any perioperative stroke or death (Executive Committee for the Asymptomatic Carotid Atherosclerosis Study, 1995). The absolute percentages of the primary outcome were 11.0% in the nonsurgical group and 5.1% in the surgical group. This translated to about a 1.2% annual absolute benefit of surgery over medical management alone over a 5-year period. This latter finding emphasizes the importance of the individual surgeon’s perioperative morbidity and mortality rates for asymptomatic carotid artery surgery. Given the modest benefits, surgical morbidity and mortality much above the accepted 3% level could result in the procedure being harmful to the patient.

REFERENCE


WARFARIN-ASPIRIN RECURRENT STROKE PREVENTION STUDY

The Warfarin-Aspirin Recurrent Stroke Prevention Study (WARSS) tested the primary hypothesis of whether warfarin (INR 1.4-2.8) would prove superior to aspirin (325 mg/d) in the prevention of recurrent ischemic stroke in patients with a prior non-cardioembolic ischemic stroke (Mohr et al, 2001). The primary hypothesis is important as many physicians prescribe warfarin, a potentially dangerous drug, for recurrent stroke prevention in patients without a cardiac source of embolism, thrombophilia, or other possible compelling indication for administration of this agent. Beyond these conditions, should warfarin be used in recurrent stroke prevention? WARSS showed that no statistically significant difference existed in the primary outcome of recurrent ischemic stroke or death within 2 years’ time for the warfarin and aspirin treatment groups. The rates of major hemorrhage were low, and the investigators concluded, therefore, that both aspirin and warfarin were reasonable treatment alternatives.

REFERENCE

WOMEN’S ESTROGEN FOR STROKE TRIAL

Observational epidemiological studies suggested that estrogen replacement therapy might reduce a woman’s risk of stroke or death during an epoch in which hormone replacement therapy had become popular for use among postmenopausal women. The Women’s Estrogen for Stroke Trial (WEST) studied whether 1 mg/d of estradiol-17ß given to postmenopausal women who had experienced recent ischemic stroke or transient ischemic attack could reduce the occurrence of stroke or death (Viscoli et al, 2001). Estrogen therapy did not reduce the risk of death alone or the risk of nonfatal stroke. In fact, women who received estrogen therapy actually had a higher risk of fatal stroke, and their nonfatal stroke was associated with slightly worse neurological and functional outcome. Therefore, estradiol was not recommended for recurrent stroke prevention in postmenopausal women.

REFERENCE


AFRICAN AMERICAN ANTIPLATELET STROKE PREVENTION STUDY

African Americans had been underrepresented in clinical trials and stroke prevention studies. The African American Antiplatelet Stroke Prevention Study (AAASPS) was the first large-scale recurrent stroke prevention study in the African American community (Gorelick et al, 2003). It was designed to determine if ticlopidine (500 mg/d) was superior to aspirin (650 mg/d) in recurrent stroke prevention. The study randomized 1809 African American non-cardioembolic ischemic stroke patients to the two treatment groups. Overall, no statistically significant difference was shown between ticlopidine-treated or aspirin-treated patients in the prevention of the composite outcome recurrent stroke, myocardial infarction, and vascular death. A nonsignificant statistical trend was shown for reduction of fatal and nonfatal stroke favoring those in the aspirin treatment group (P = .08 by log-rank test). The occurrence of serious adverse events was generally comparable in the two treatment groups, but one case of serious thrombocytopenia occurred in the ticlopidine group. In conclusion, based on efficacy and side effect profiles, aspirin was regarded as a better treatment than ticlopidine for aspirin-tolerant African American patients with non-cardioembolic ischemic stroke.

REFERENCE


VITAMIN INTERVENTION FOR STROKE PREVENTION

Vitamins are a popular supplement among persons concerned about their cardiovascular and general health. Administration of B-complex vitamins has been shown to lower homocysteine, a factor thought to be related to cardiovascular and stroke risk. In the Vitamin Intervention for Stroke Prevention trial (VISP), high and lower doses of folic acid, pyridoxine, and cobalamin were administered to persons with nondisabling cerebral infarction (Toole et al, 2004). These persons were then followed to determine the occurrence of the primary outcome of recurrent cerebral infarction or secondary outcomes of coronary heart disease and death. The Vitamin Intervention for Stroke Prevention trial showed that homocysteine could be successfully lowered by a total mean reduction of 2 µmol/L greater in the high-dose treatment group compared with the low-dose treatment group. There was, however, no treatment effect on any end point. The association of total homocysteine with vascular risk suggests the need for further exploration of the hypothesis in longer trials among different populations with elevated homocysteine.
REFERENCE


WARFARIN-ASPIRIN SYMPTOMATIC INTRACRANIAL DISEASE TRIAL

The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial compared oral anticoagulation therapy with warfarin (INR 2 to 3) to aspirin (1300 mg/d) for prevention of ischemic stroke and brain hemorrhage or death from vascular causes other than stroke in patients with 50% to 99% symptomatic stenosis of a major intracranial artery. (Chimowitz et al, 2005). Relatively little information about medical management of symptomatic intracranial large artery stenosis has been available. The WASID trial was halted by the National Institutes of Health on July 18, 2003, based on a recommendation of the external safety committee relating to concerns of safety of patients assigned to warfarin therapy. In the main phase analysis from this study, warfarin was associated with significantly higher rates of adverse events and provided no major benefit over aspirin. The authors concluded that aspirin should be used in preference to warfarin for patients with symptomatic intracranial occlusive disease of a major artery. In an accompanying editorial Koroshetz (2005) highlighted the points that symptomatic intracranial atherosclerosis is an aggressive vascular disease, aspirin is an imperfect therapy, and anticoagulation is promising but difficult to achieve.

REFERENCES


Main phase results of the Warfarin Aspirin Symptomatic Intracranial Disease trial of intracranial occlusive disease of a major cerebral artery comparing warfarin and aspirin.


STROKE PREVENTION IN ATRIAL FIBRILLATION

The Stroke Prevention in Atrial Fibrillation (SPAF) studies consisted of six multicenter clinical trials assessing antithrombotic therapies for the prevention of stroke in nonvalvular atrial fibrillation (Hart et al, 2003; SPAF Writing Committee for the Stroke Prevention in Atrial Fibrillation Investigators, 1990, 1991, 1994, 1996, and 1998). Investigators followed 3950 participants for 7100 patient years, during which time 247 had strokes. Overall, the SPAF studies established the safety and efficacy of warfarin therapy (INR 2 to 3) over placebo or aspirin for stroke reduction in persons with atrial fibrillation, provided data on intracranial bleeding risks in elderly persons (greater than 75 years), and identified persons at low risk of stroke who might be treated with aspirin therapy.

REFERENCES

ANTIPHOSPHOLIPID ANTIBODIES AND STROKE STUDY

The Antiphospholipid Antibody and Stroke Study (APASS) was a prospective cohort study within the Warfarin Aspirin Recurrent Stroke Study (WARSS) designed to assess the outcomes associated with antiphospholipid antibody (aPL) positivity within each WARSS treatment group, aspirin or warfarin (Levine et al, 2004). Overall, the presence of aPL in the form of either lupus anticoagulant antibodies or anticardiolipin antibodies did not predict increased risk of subsequent vascular occlusive events over a 2-year period or a differential response to aspirin or warfarin treatment.

REFERENCE


A preplanned WARSS collaborative add-on study to determine the role of antiphospholipid antibodies in the prediction of subsequent vascular events and possible differential effects of warfarin or aspirin on the occurrence of subsequent vascular events.

PATENT FORAMEN OVALE IN CRYPTOGENIC STROKE STUDY

The Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS) was a collaborative substudy of WARSS in which 630 stroke patients who participated in WARSS and who had received transthoracic echocardiography as part of their evaluation were recruited (Homma et al, 2002). The study was designed to look at a number of recurrent adverse event rates germane to ischemic stroke patients based on underlying cardiac comorbidity (e.g., presence or absence of patent foramen ovale [PFO], the primary outcome of interest to neurologists; valvular strands on the mitral or aortic valve) treated with either aspirin or warfarin. Overall, the average annual risk of stroke was estimated to be 7.4% among persons with PFO and 7.7% among those without PFO. Although a higher prevalence of large PFO occurred among persons with cryptogenic stroke, no increased risk of recurrent stroke occurred based on PFO size. Furthermore, the rate of recurrent stroke or death in persons with PFO was not significantly different whether they were treated with aspirin or warfarin. The stroke or death rate, however, was about 50% lower among those with cryptogenic stroke who received warfarin.

REFERENCE


A Warfarin Aspirin Recurrent Stroke Study (WARSS) substudy to determine the role of patent foramen ovale and other cardiac conditions in first and recurrent stroke risk and the effect of warfarin and aspirin in reducing stroke risk in these patients.