Recommended Readings

This column is an idiosyncratic group of ten papers for 2006 that have been arbitrarily selected by me as potentially significant or at least intriguing to clinical neurologists interested in cerebrovascular disease. Since hemorrhagic stroke comprises approximately 20 percent of all stroke, 2/10 articles listed below deal with intracerebral or subarachnoid hemorrhage. There are countless numbers of equally significant papers this past year and I make no attempt to present this as a comprehensive list.

Michael J. Schneck, MD, FAAN, Stroke Section Communications Workgroup Leader. If you have any questions or comments, please email me at mschneck@lumc.edu


NOTES: Update of the AHA/ASA guidelines with the latest recommendations and guidelines. A ‘must read’ for all neurologists.


“In patients with recent stroke or TIA and without known coronary heart disease, 80 mg of atorvastatin per day reduced the overall incidence of strokes and of cardiovascular events, despite a small increase in the incidence of hemorrhagic stroke. The 5-year absolute reduction in stroke risk was 2.2 percent; the atorvastatin group had 218 ischemic strokes and 55 hemorrhagic strokes, whereas the placebo group had 274 ischemic strokes and 33 hemorrhagic strokes. The five-year absolute reduction in the risk of major cardiovascular events was 3.5 percent”

NOTES: This paper supports the previous assumptions that lipid lowering is appropriate in all stroke patients and that stroke patients should be treated with the same level of aggressive care as MI patients.


The study was stopped early because of clear evidence of superiority of oral anticoagulation therapy. There were 165 primary events in patients on oral anticoagulation therapy (annual risk 3.93%) and 234 in those on clopidogrel plus aspirin (annual risk 5.60%; relative risk 1.44 (1.18-1.76; p=0.0003).

NOTES: Warfarin remains the mainstay in the prevention of atrial fibrillation related strokes.


Mean follow-up in this study was 3.5 years and the median dose of aspirin was low at 75 mg daily (range 30-325); extended-release dipyridamole was used by 83% (n=1131) of patients on the combination regimen. Primary outcome events arose in 173 (13%) patients on aspirin and dipyridamole and in 216 (16%) on aspirin alone (hazard ratio 0.80, 95% CI 0.66-0.98; absolute risk reduction 1.0% per year, 95% CI 0.1-1.8).
NOTES: This trial supports the use of combination antiplatelet therapy with dypridamole and aspirin as compared with low dose aspirin alone with a small but significant benefit.


Among 82 patients (mean NIHSS 7.1 [+/-6.3 SD]), the only independent outcome predictors were age and stroke severity. Neither DWI lesion volume nor apparent diffusion coefficient nor the previously described Three-Item Scale predicted outcome independently. Comparison with previous studies suggested that DWI may predict outcome only in patients with more severe cortical ischemic strokes.

NOTES: This small trial continues to support clinical factors as the major predictor of outcome in stroke and re-emphasizes the importance of the *clinical* assessment and examination of stroke patients.


“This report provides a thorough analysis of the stroke finding ([from the WHI] using the final results from the completed trial database. METHODS AND RESULTS: The WHI Estrogen Alone hormone trial is a multicenter, double-blind, placebo-controlled, randomized clinical trial in 10,739 women aged 50 to 79 years who were given daily conjugated equine estrogen (CEE; 0.625 mg; n=5310) or placebo (n=5429). During an average follow-up of 7.1 years, there were 168 strokes in the CEE group and 127 in the placebo group; 80.3% of strokes were ischemic. For all stroke the intention-to-treat hazard ratio [HR] (95% CI) for CEE versus placebo was 1.37 (1.09 to 1.73). The HR (95% CI) was 1.55 (1.19 to 2.01) for ischemic stroke and 0.64 (0.35, 1.18) for hemorrhagic stroke. The HRs indicate excess risk of ischemic stroke was apparent in all categories of baseline stroke risk, including younger and more recently menopausal women and in women with prior or current use of statins or aspirin.

NOTES: CEE increases the risk of ischemic stroke in generally healthy postmenopausal women in all subgroups examined. The previous WEST study (from my fellowship mentor, the late Lawrence Brass and his colleagues similarly demonstrated that estrogen therapy did not decrease the risk of recurrent stroke.


“Among the 1699 subjects included in the efficacy analysis, NXY-059 significantly improved the overall distribution of scores on the modified Rankin scale, as compared with placebo (P=0.038 by the Cochran–Mantel–Haenszel test). The common odds ratio for improvement across all categories of the scale was 1.20 (95 percent confidence interval, 1.01 to 1.42)…NXY-059 did not improve neurologic functioning as measured according to the National Institutes of Health Stroke Scale (NIHSS)….Likewise, no improvement was observed according to the Barthel index (P=0.14). In a post hoc analysis of patients who also received alteplase, NXY-059 was associated with a lower incidence of any hemorrhagic transformation (P=0.001) and symptomatic intracranial hemorrhage (P=0.036)”

NOTES: The SAINT II study has recently been completed and results should be forthcoming soon. It remains to be seen whether there will be similar (or hopefully more robust) findings for NXY-059 observed in the second study. If SAINT-II is at all positive, then NXY-059 would be the first neuroprotective agent to have any demonstrated efficacy in acute ischemic stroke.

8. Huttner HB, Schellinger PD, Hartmann M, et al.. **Hematoma growth and outcome in treated neurocritical care patients with intracerebral hemorrhage related to oral anticoagulant therapy:**

“This small retrospective study of 55 patients compared those who received prothrombin complex concentrates (PCC) alone or in combination with fresh frozen plasma (FFP) or vitamin K (VAK) (n=31); patients treated with FFP alone or in combination with VAK (n=18); and patients who received VAK as a monotherapy (n=6). Incidence and extent of hematoma growth were significantly lower in patients receiving PCCs (19%/44%) compared with FFP (33%/54%) and VAK (50%/59%). However, this effect was no longer seen between PCC- and FFP-treated patients if international normalized ratio (INR) was completely reversed within 2 hours after admission. The overall outcome was poor. Predictors for hematoma growth were an increased INR after 2 hours, whereas administration of PCCs was significantly protective in multivariate analyses. Overall, PCC was associated with a reduced incidence and extent of hematoma growth compared with FFP and VAK. This effect seems to be related to a more rapid INR reversal.”

NOTES: Recombinant Factor VIIa is being studied in a second clinical trial for acute intracerebral hemorrhage with 4 hours of symptom onset. The above trial suggests that other agents might be studied as well.


“One hundred and thirteen patients with aneurysmal subarachnoid hemorrhage were enrolled in the study and were randomized to receive either magnesium sulfate (loading 10 mg/kg followed by 30 mg/kg daily) or nimodipine (48 mg/d) intravenously until at least postoperative Day 7. … One hundred and four patients met the study requirements. In the magnesium group (n = 53), eight patients (15%) experienced clinical vasospasm and 20 (38%) experienced transcranial Doppler/angiographic vasospasm compared with 14 (27%) and 17 (33%) patients in the nimodipine group (n = 51). If clinical vasospasm occurred, 75% of the magnesium-treated versus 50% of the nimodipine-treated patients experienced cerebral infarction resulting in fatal outcome in 37 and 14%, respectively. Overall, the rate of infarction attributable to vasospasm was virtually the same (19 versus 22%). There was no difference in outcome between groups.

NOTES: Magnesium is currently being studied for acute ischemic stroke in the FAST-Mag study. This intriguing study suggests that magnesium may have wider applicability in hemorrhagic stroke as well.


“The observed number of vascular events during the birthday was higher than the expected daily number of visits for stroke (87 vs 67; p = 0.009), TIA (58 vs 44; p = 0.02), and AMI (97 vs 80; p = 0.027) but not for selected control conditions (asthma, appendicitis, head trauma). Vascular events were more likely to occur on birthday (242 vs 191; odds ratio [OR] = 1.27). … Stress associated with birthdays may trigger vascular events in patients with predisposing conditions.”

NOTES: This last study is a reminder that birthdays are not always happy…..